Eurosurveillance

Volume 14, Issue 45 - 12 November 2009

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EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

Editorials

Antibiotic resistance in Europe: the challenges ahead

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This article was published on 12 November 2009.
Citation style for this article: ECDC Antimicrobial Resistance and Healthcare-Associated Infections Programme. Antibiotic resistance in Europe: the challenges ahead. Euro Surveill. 2009;14(45):pii=19405. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19405

On 18 November 2009, the second European Antibiotic Awareness Day will be celebrated throughout Europe. This European public health initiative coordinated by the European Centre for Disease Prevention and Control (ECDC) aims to communicate about the importance of prudent use of antibiotics in order to turn the tide on antibiotic resistance. Last year's campaign focused on antibiotic awareness of the general public. Thirty-two European countries participated producing information materials and implementing activities ranging from press conferences to national media campaigns [1]. The main focus of this year's European Antibiotic Awareness Day campaign is to work with primary care prescribers to promote appropriate use of antibiotics, with particular attention to respiratory tract infections such as common colds and flu. Campaign materials, including factsheets and leaflets, have been prepared together with professional organisations representing primary care prescribers and a multi-lingual website has been developed (http://antibiotic.ecdc.europa.eu).

Prudent use of antibiotics is not the only strategy for fighting antibiotic resistance. Good infection control practices, including hand hygiene as well as the screening and isolation of infected patients are necessary to prevent the spread of resistant bacteria. Several European countries have or have had national or regional campaigns on hand hygiene [2], but improving hand hygiene practices remains a challenge in many countries. A European Union (EU) Council Recommendation on patient safety, including the prevention and control of healthcare-associated infections has been adopted by EU Health Ministers on 9 June 2009 and lists a series of actions in this area [3]. ECDC will provide support by developing guidance documents for prevention of control of these infections.

Developing and marketing of new antibiotics with novel mechanisms of action represents a further essential strategy against antibiotic resistance as resistance inevitably builds over time. A recent report from ECDC and the European Medicines Agency (EMEA) identified a gap between increasing prevalence of multidrug-resistant bacteria in the EU and the current state of the development pipeline for new antibiotics [4]. This topic is one of the priorities of the current Swedish Presidency of the EU and was discussed at the conference "Innovative Incentives for Effective Antibacterials" [5].

Primary care accounts for 80 to 90% of all antibiotic prescriptions in humans, which is why public awareness campaigns on the prudent use of antibiotics generally focus on primary care. In the United States (US), the Centers for Disease Control and Prevention (CDC) are coordinating the campaign "Get Smart: Know When Antibiotics Work" [6], which is also focusing on the general public and healthcare providers. At a recent summit on 3 November 2009, the US and the EU agreed to establish a transatlantic task force on urgent antimicrobial resistance issues [7]. ECDC and the CDC are already cooperating closely on their public awareness campaigns on the prudent use of antibiotics. While the CDC are already preparing a campaign to address hospital prescribers, European Antibiotic Awareness Day will in 2010 also focus on prudent use of antibiotics in hospitals. ECDC is also working closely with the World Health Organization Regional office Europe to promote participation in the campaign of European countries that are not members of the EU.

This issue of Eurosurveillance highlights two topics that relate to antibiotic resistance and infection control in hospitals. The first one is *Clostridium difficile*. Hensgens *et al.* [8] report on a shift in the PCR ribotypes identified in the Netherlands with PCR ribotype 027 almost disappearing whereas Arvand *et al.* [9] report that this PCR ribotype is still prevalent within Hesse, one federal state of Germany. As of now, the only available pan-European data for this micro-organism are from the European *C. difficile* infection survey (ECDIS) that was performed in November 2008 [10]. This survey highlighted the need for increased capacity building for the detection, typing and surveillance of *C. difficile* infections in Europe and ECDC will provide support to these activities.

The second topic is the emergence of totally or almost totally resistant bacteria in Europe. Last year, Souli *et al*. published a review on this topic in Eurosurveillance [11]. In this issue, a survey among European intensive care physicians shows that about one half had seen at least one patient infected by such bacteria and about one fifth had seen three patients or more in the preceding six months [12]. Studies are now needed to assess the extent of the spread of totally or almost totally resistant bacteria in Europe and to determine the risk factors for colonization and infection. In the meantime, ECDC will prepare interim guidance documents for prevention and control of these bacteria.

Antibiotic resistance is also an issue in zoonotic infections, foods, food animals, pets and agriculture and a joint opinion on antimicrobial resistance in zoonoses from several EU agencies has recently been finalised [13].

Antibiotic resistance is a moving target. While Europe is obviously making progress towards increased awareness about prudent use of antibiotics and the prevention and control of antibiotic-resistant bacteria and healthcare-associated infections, all the issues highlighted in this editorial deserve our full attention. These are the challenges ahead.

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Experience of European intensive care physicians with infections due to antibiotic-resistant bacteria, 2009

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This article was published on 12 November 2009.
Citation style for this article: Lepape A, Monnet DL, on behalf of participating members of the European Society of Intensive Care Medicine (ESICM). Experience of European intensive care physicians with infections due to antibiotic-resistant bacteria, 2009. Euro Surveill. 2009;14(45):pii=19393. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19393

A survey was performed among European intensive care physicians to obtain information about their perception and experience with selected antibiotic-resistant bacteria. Seventy-eight out of 95 (82%) participants considered having to deal with infections due to antibiotic-resistant bacteria in the intensive care unit where they work was a major or significant problem. Methicillin-resistant *Staphylococcus aureus* (MRSA) and third-generation cephalosporin-resistant *Enterobacteriaceae* were the most frequently reported antibiotic-resistant bacteria with 69 (73%) and 67 (71%) participants reporting having treated at least one patient with such an infection during the preceding six months, respectively. Antibiotic-resistant Gram-negative bacteria, including carbapenem-resistant *Enterobacteriaceae*, were more frequently reported than any selected antibiotic-resistant Gram-positive bacteria, with the exception of MRSA. Fifty (53%) participants declared having treated at least one patient infected with a bacterium totally or almost totally resistant to available antibiotics during the past six months, with 8 participants having treated more than 10 such patients and 13 having treated from 3 to 10 such patients.

Introduction

Antibiotic resistance is a threat to public health and compromises appropriate therapy of infected patients, in particular for infections in the most severely ill in hospitals [1,2]. Increasingly, intensive care physicians in Europe and elsewhere are confronted with patients infected by bacteria for which limited or no adequate therapeutic options are available [2-4]. Data on the situation of antibiotic resistance in Europe are provided by the European Antimicrobial Resistance Surveillance System (EARSS) [5], however these data are not specific for patients in intensive care units (ICUs). There are studies on antibiotic resistance in European intensive care patients, but these are limited to only a few ICUs and countries [1,6-7]. Additionally, there is little data on infections with bacteria that are totally or almost totally resistant to antibiotics that are currently emerging in Europe [8]. In an attempt to obtain information on the perception and experience of European intensive care physicians on infections caused by antibiotic-resistant bacteria, a survey was conducted through the European Society of Intensive Care Medicine (ESICM) among its members in 2009. We report here the first results of this survey.

Methods

The survey was designed by the European Centre for Disease Prevention and Control (ECDC) with input from an ECDC/European Medicines Agency (EMEA) Joint Working Group [9] and then proposed to the Scientific Committee of ESICM. The survey included questions about the experience of the respondent with intensive care medicine and antibiotic prescribing, as well as about the ICU in which they work. It also included questions about perception of the respondent of the problem of antibiotic resistance and the number of patients that were treated, during the preceding six months in the ICU where they work, for infections caused by each of the antibiotic-resistant bacteria listed in the table. These antibiotic-resistant bacteria were selected because they are, in most cases, multidrug-resistant.

Participants gave answers on their experience during the past six months following a semi-quantitative scale: “often” (> 10 patients), “sometimes” (3-10 patients), “rarely” (1-2 patients) and never. The survey was endorsed by ESICM through its European Critical Care Network in March 2009. It was then posted on the ESICM website in its section “Survey of the month” in the beginning of April 2009 and was closed on 8 June 2009.

Results

Characteristics of participants

After excluding responses issued from participants from non-European countries or non-ESICM members, 95 responses were analysed. Responses were obtained from European ESICM members from 24 countries: Austria (2 participants), Belgium (5), Croatia (2), Denmark (2), France (4), Germany (8), Greece (3), Hungary (1), Ireland (1), Israel (1, ESICM includes this country among European countries), Italy (14), Lithuania (1), Luxembourg (1), Montenegro (1), Netherlands (1), Portugal (12), Romania (5), Serbia (1), Slovakia (1), Spain (12), Sweden (2), Switzerland (1) and United Kingdom (14).

Among the participants, the median time since graduation as MD was 20 years (25th-75th percentiles: 13-27 years). Seventy-nine (83%) participants were intensive care medicine specialists with a median time since specialisation of 11 years (25th-75th percentiles: 4-18 years). Eleven participants were still in training and five had a different specialty than intensive care medicine. Seventy-five (79%) ICUs were medico-surgical ICUs with a median

size of 10 beds (25th-75th percentiles: 7-16 beds) and a median of 510 admissions per year (25th-75th percentiles: 350-850). To the question "How often do you personally prescribe antibiotic therapy to ICU patients?", 88 (93 %) responded "commonly (> 10 patients per week)" or "often (≥3 patients per week)".

Perception of and experience with antibiotic-resistant bacteria

Having to deal with infections due to antibiotic-resistant bacteria in the ICU where they work was considered as a major or significant problem by 78 (82%) participants. The experience of the participants of treating patients with infections due to the selected antibiotic-resistant bacteria is summarised in the Figure. Among Gram-positive bacteria, methicillin-resistant *Staphylococcus aureus* (MRSA) was the most frequently reported with 69 (73%) participants reporting having treated at least one patient with an MRSA infection during the preceding six months. Vancomycin-resistant *Enterococcus* spp. (VRE) and penicillin-resistant *Streptococcus pneumoniae* were much less frequently reported, and vancomycin-resistant or -intermediate *S. aureus* (VRSA/VISA) was the least frequently reported antibiotic-resistant

Table

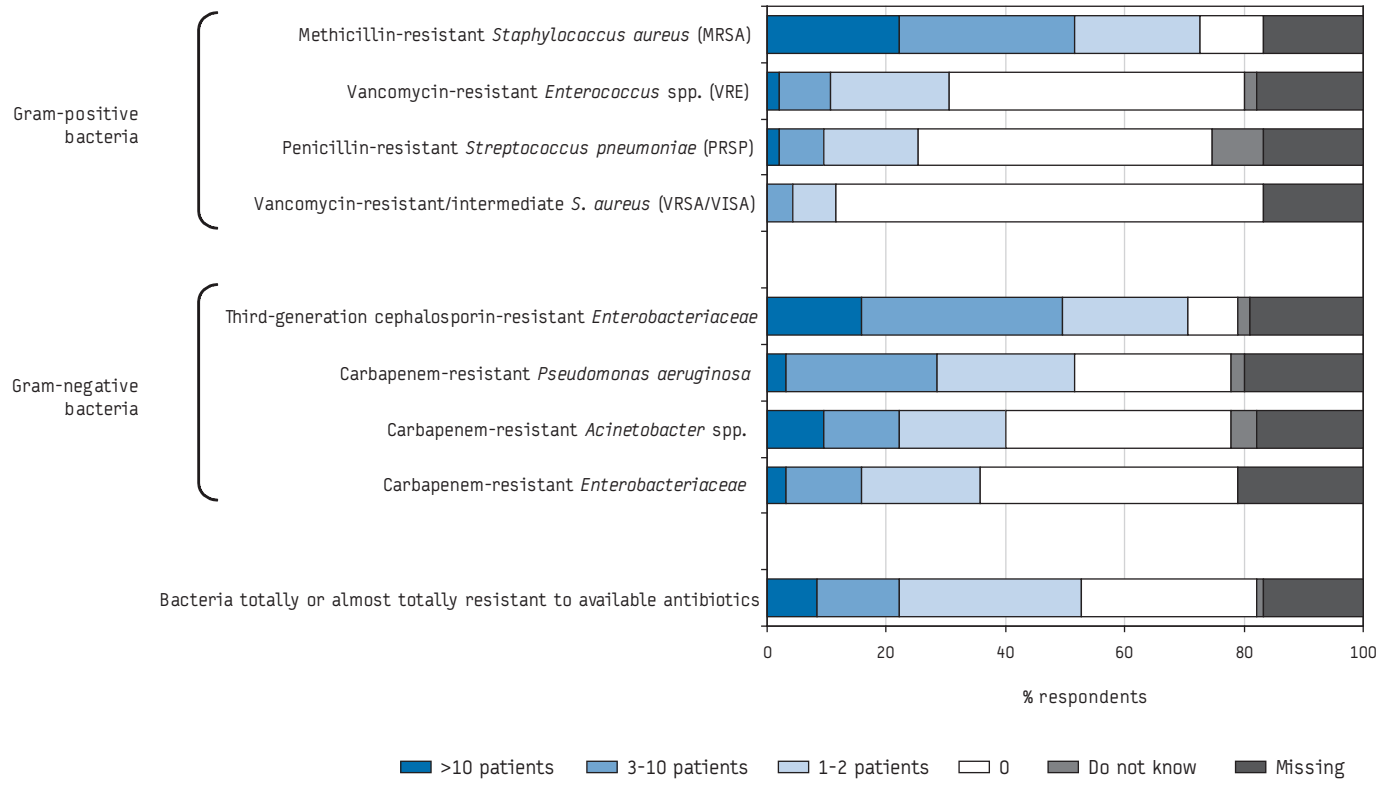
Antibiotic-resistant bacteria selected for the European intensive care physicians survey, 2009

Gram-positive bacteria	Methicillin-resistant *Staphylococcus aureus* (MRSA)
	Vancomycin-resistant/intermediate *S. aureus* (VRSA/VISA)
	Vancomycin-resistant *Enterococcus* spp. (VRE)
	Penicillin-resistant *Streptococcus pneumoniae*
Gram-negative bacteria	Third-generation cephalosporin (cefotaxime or ceftazidime or ceftriaxone)-resistant *Enterobacteriaceae* (e.g. *Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp.)
	Carbapenem (imipenem or meropenem)-resistant *Enterobacteriaceae*
	Carbapenem-resistant *Pseudomonas aeruginosa*
	Carbapenem-resistant *Acinetobacter* spp.
Bacteria totally or almost totally resistant to available antibiotics*	

*Any Gram-positive or Gram-negative bacteria considered as totally or almost totally resistant to available antibiotics based upon the appreciation of the participant. In addition, the participant was asked to specify the name of these bacteria.

Figure

Percentage of participants who reported having treated patients with infections due to selected antibiotic-resistant bacteria during the past six months, 2009 (n=95 participants)



Gram-positive bacteria with only 11 (12%) participants reported having treated such patients during the preceding six months. Among Gram-negative bacteria, third-generation cephalosporin-resistant *Enterobacteriaceae* were the most frequently reported with 67 (71%) participants reporting having treated at least one patient with such an infection during the preceding six months. Other selected antibiotic-resistant Gram-negative bacteria were less frequently reported. The least reported antibiotic-resistant Gram-negative bacterium, i.e. carbapenem-resistant *Enterobacteriaceae*, was more frequently reported than any selected antibiotic-resistant Gram-positive bacteria with the exception of MRSA (Figure). Forty-eight (51%) participants reported having treated at least three patients in two or more of the selected categories of antibiotic-resistant bacteria during the preceding six months, thus showing that antibiotic resistance problems faced by the participants in the unit where they work are often not limited to one single antibiotic-resistant bacterium.

Finally, 50 participants declared having treated at least one patient infected with a bacterium totally or almost totally resistant to available antibiotics during the past six months. Moreover, 8 participants declared having treated more than 10 such patients and 13 participants declared having treated from 3 to 10 such patients during the past six months (Figure). Forty-two participants mentioned the names of these bacteria totally or almost totally resistant to available antibiotics or the names of any other antibiotic-resistant bacteria that posed a problem when considering patient therapy in the ICU where they work. Among the 55 bacteria mentioned, most were Gram-negative bacteria: *Pseudomonas* spp. (mentioned 23 times, mostly *P. aeruginosa*), *Acinetobacter* spp. (17 times), *Stenotrophomonas maltophilia* (9 times) and *Enterobacteriaceae* (5 times). *Enterococcus* spp. was only cited once.

Discussion

In hospitals, intensive care units are considered as areas where antibiotic resistance problems are the largest due to the combination of multiple factors. These factors include the concentration of severely ill patients requiring specialised care, the high frequency of use of medical devices and the high frequency of antibiotic treatment [1]. Not surprisingly, most intensive care physicians that participated in the survey felt that antibiotic resistance was a major or significant problem in their practice.

Overall, the picture of antibiotic resistance in Europe provided by this study is similar to that provided by EARSS [5], with MRSA and third-generation cephalosporin-resistant *Enterobacteriaceae* being the most frequently antibiotic-resistant bacteria encountered by European intensive care physicians. The survey also confirmed the observation of a recent joint technical report of ECDC and EMEA which showed that, with the exception of MRSA, the burden of antibiotic resistance in Europe was now mostly due to antibiotic-resistant Gram-negative bacteria [9]. In addition, it showed that many European intensive care physicians are facing patients with infections due to bacteria, mostly Gram-negative, totally or almost totally resistant to available antibiotics. The ECDC/EMEA joint technical report showed that there were very few new antibiotics with a novel mechanism of action in development to meet the challenge of multidrug-resistant bacteria, in particular to treat infections due to Gram-negative bacteria [9]. Patients with infections due to carbapenem-resistant Gram-negative bacteria often require the use of old and toxic antibiotics such as colistin [3, 8].

This study has several limitations. Firstly, it is based on the voluntary declaration of a small fraction of the more than 5,000 ESICM members. This is likely to have resulted in selection bias towards the more concerned ESICM members, in particular from southern Europe. Although the survey instructions explicitly mentioned that only one intensive care physician per ICU should participate in the survey, we cannot exclude duplicate participation from the same ICU. Finally, participants had to answer retrospectively on their experience during the preceding six months, which may have resulted in recall bias and may be the reason for approximately 20 % of missing information. The data presented here, however, are likely to be an underestimate of the situation in the included ICUs since most participants with missing information on specific antibiotic-resistant bacteria considered infections with antibiotic-resistant bacteria in the ICU where they work as a major or significant problem. Despite these limitations, the study provides a first snapshot, based on recalled recent experience, of the current antibiotic resistance problems faced by European intensive care physicians when treating patients. It also highlighted the problem of infections due to totally or almost totally resistant bacteria, which are not covered by existing surveillance systems. More comprehensive studies are now needed to assess the extent of the prevalence of such infections with totally or almost totally resistant bacteria as well as to determine the risk factors for colonization and infection with these bacteria. In the meantime, intensive care and other physicians should be made aware of their current emergence in Europe.

Acknowledgements

The authors thank ESICM members who participated in the survey as well as Professor Jean-Daniel Chiche, President of the ESICM Scientific Committee and Professor Claude Martin, past President of the Infectious Diseases Section of ESICM. They would also like to thank members of the ECDC/EMEA Joint Working Group [9] for their input when designing the survey and preparing the questionnaire.

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Decrease of hypervirulent Clostridium difficile PCR ribotype 027 in the Netherlands

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This article was published on 12 November 2009.
Citation style for this article: Hensgens MP, Goorhuis A, Notermans DW, van Benthem BH, Kuijper EJ. Decrease of hypervirulent Clostridium difficile PCR ribotype 027 in the Netherlands. Euro Surveill. 2009;14(45):pii=19402. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19402

After the first outbreaks of *Clostridium difficile* PCR ribotype 027 (North American pulsed-field type 1, restriction endonuclease analysis group BI) in the Netherlands in 2005, a national surveillance programme for *C. difficile* infection (CDI) was started. Furthermore, national guidelines were developed to rapidly recognise type 027 infections and prevent further spread. The mean incidence of CDI measured in 14 hospitals remained stable throughout the years: an incidence of 18 per 10,000 admissions was seen in 2007 and 2008. Between April 2005 and June 2009 a total of 2,788 samples were available for PCR ribotyping. A decrease was seen in the number and incidence of type 027 after the second half of 2006. In the first half of 2009, the percentage of type 027 isolates among all CDI decreased to 3.0%, whereas type 001 increased to 27.5%. Type 014 was present in 9.3% of the isolates and *C. difficile* type 078 slightly increased to 9.1%. We conclude that currently there is a significant decrease in type 027-associated CDI in the Netherlands.

Since the new hypervirulent strain of *Clostridium difficile*, PCR ribotype 027, North American pulsed-field type 1 (NAP1), restriction endonuclease analysis (REA) group BI, was found in the United States and Canada in 2001, a large number of countries worldwide reported *C. difficile* infections (CDI) due to this type [1,2]. Several reports indicated that CDI due to type 027 is associated with a higher morbidity and mortality and also has the tendency to relapse more frequently [3-6]. An overview published in July 2008 revealed that type 027 was detected in 16 European countries and was associated with outbreaks in Belgium, Finland, France, Germany, Ireland, Luxembourg, the Netherlands, Switzerland and the United Kingdom [7]. As of July 2008, outbreaks have also been reported in Austria [8] and Denmark [9].

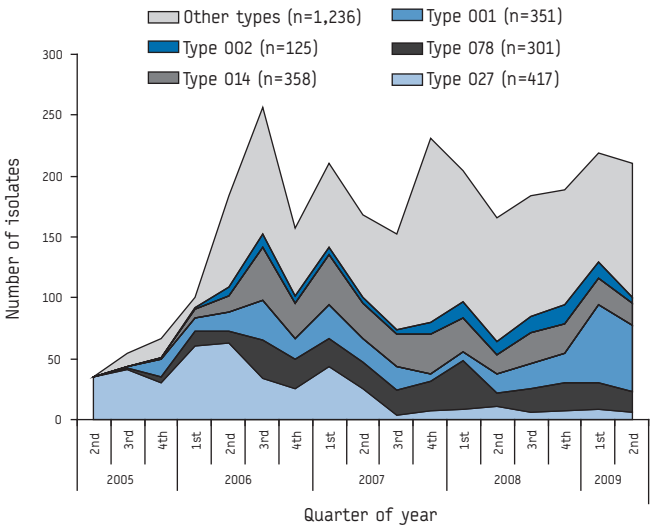
Soon after the first outbreaks in the Netherlands in 2005, a national surveillance programme for *C. difficile* was initiated by the Leiden University Medical Centre (LUMC) and the Centre for Infectious Disease Control of the National Institute for Public Health and the Environment. All medical microbiologists in the Netherlands were requested to send *C. difficile* isolates to the Dutch national reference laboratory at the LUMC for rapid PCR ribotyping and characterisation in case of an outbreak (more than two CDI cases within one week in one department) or when a patient suffered from severe CDI. In addition, a prospective, three year-long surveillance study of the incidence of CDI and the distribution of the *C. difficile* PCR ribotypes was started in 14 Dutch hospitals in June 2006.

In the period between April 2005 and June 2009, a total of 3,137 samples were submitted to the reference laboratory, of which 89% (n=2,788) were available for PCR ribotyping. Of those 2,788 samples, 51% had been submitted by medical microbiologists because of either severe disease or a CDI outbreak, whereas the remaining 49% were part of the national surveillance study. Since no difference in the distribution of various PCR ribotypes was found between the two surveillance systems, we represent the data combined. The reason for this equal distribution is that most hospitals that encountered an outbreak or a case of severe CDI, continued to submit samples on a regular basis thereafter.

The Figure depicts the distribution of the five most common PCR ribotypes in the Netherlands between April 2005 and June 2009. Although the total number of submitted samples increased from 35 in the second quarter of 2005 to a steady number between 150 and 250 after the first quarter of 2006, a decrease in the number of type 027 isolates has been observed since the second half of 2006. In the 14 hospitals participating in the continuous surveillance, a

Figure

***C. difficile* PCR ribotypes in the Netherlands, April 2005 – June 2009 (n=2,788)**



decrease in the quarterly incidence of type 027 (number of isolates per number of admissions) was seen. This decrease was confirmed in linear regression and remained significant after adjustment for the number of samples that we received (p=0.03).

In the first half of 2009, type 027 was found in 3.3% of the 430 submitted samples. Type 001 (n=118; 27.4%) was the most common type, followed by type 014 (n=40; 9.3%), 078 (n=39; 9.1%) and 002 (n=19; 4.4%). We also encountered a number of isolates that did not match a PCR ribotype in our database and belonged to different, yet unknown types (n=49; 11.4%). These are currently subject of further investigation. Finally, of all isolates in the first two quarters of 2009, 35.1% belonged to 41 different PCR ribotypes, which were present in small numbers. Types 015 (n=15; 3.5%), 056 and 087 (both 2.6%), 017 and 046 (both 1.9%) were the five most frequently found types among those. The types that could not be matched in our database and the 41 less common types were combined in the group 'other types', as displayed in the Figure.

To determine the incidence of CDI in the Netherlands, we used the continuous surveillance data only. From the beginning of 2007 to the end of 2008, the mean incidence was 18 per 10,000 hospital admissions, ranging from 8 to 35 per 10,000 admissions among the 14 hospitals. These numbers are in line with a previous study performed in the Netherlands, which showed an incidence of 16 per 10,000 admissions [10]. A nationwide incidence study in neighbouring Belgium revealed a similar (median) incidence of 15 per 10,000 admissions [11].

Discussion and conclusions

To our knowledge, the Netherlands are the first European country with a documented decrease of the hypervirulent type 027. The detection of type 027 in 2005 resulted in a number of measurements taken on a national level. Most hospitals which experienced CDI due to type 027 followed the principles of the infection control guideline supported by the European Centre for Disease Prevention and Control (ECDC) to limit the spread of *C. difficile*, emphasising the importance of responsible use of antimicrobial drugs in conjunction with proper environmental disinfection, compliance with hand hygiene, protective clothing, education of staff and single-room isolation or cohorting of CDI patients [12,13]. Although the role of fluoroquinolones as an important predisposing factor for CDI due to type 027 has been recognised in several outbreaks [13,14], the observed decrease in incidence of type 027 in the Netherlands is not related to a change of nationwide use of fluoroquinolones since this remained stable in hospitals [15].

The relatively high frequency of type 001 in Dutch hospitals is not exceptional and has recently also been reported in southern Germany, Ireland, Luxembourg and the United Kingdom [7,16]. Type 014 is also frequently found in other European countries: it is the most common strain found in Hungary (2002-2004), Norway and Sweden (2008), and the second most common strain in Austria (2006) and Poland (2002-2003) [7,8,17,18]. An increase of type 078 had been noticed previously in the Netherlands [19]. In the quarterly data presented here, the increase is also seen: in the first trimester of 2008 19% of all samples consisted of type 078. After this peak, however, the contribution of type 078 decreased and it became the third most common strain in the Netherlands. Also in several other European countries type 078 is increasingly observed [7]. This type is a predominant strain in some farm animals (especially in pigs and dairy calves) and has recently been found in retail meat in North America [20]. The genetic similarity between animal and human type 078 strains as demonstrated by the highly discriminatory multilocus variable number of tandem repeats analysis (MLVA), also suggests a possible common source of animal and human type 078 strains. Type 078 and type 027 have similar virulence factors (positive for toxin A, B and binary toxin, and a dysfunctional toxin regulator gene). Furthermore, they resemble CDI in their clinical presentation: both cause severe diarrhoea in 40% of cases. A complicated course is seen less often in CDI caused by type 078, possibly because type 078 is observed in a younger population, with a higher frequency of community-associated CDI [19].

In conclusion, CDI caused by the hypervirulent 027 strain is now observed less frequently in the Netherlands, while the 'common' types 001 and 014 remain prominently present in the Dutch hospitals. Type 078 is currently the third most common PCR ribotype in the Netherlands and other European countries, whereas its occurrence before 2005 was very rare. More research is needed on the source of this strain and a possible exchange between animals and humans.

Acknowledgements

We thank all medical microbiologists and infection control practitioners who participated in this study. C Harmanus is acknowledged for technical support at the Reference Laboratory.

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A simple mathematical approach to deciding the dosage of vaccine against pandemic H1N1 influenza

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This article was published on 12 November 2009.
Citation style for this article: Nishiura H, Iwata K. A simple mathematical approach to deciding the dosage of vaccine against pandemic H1N1 influenza. Euro Surveill. 2009;14(45):pii=19396. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19396

Results from early clinical trials have shown that a single dose of pandemic H1N1 influenza vaccine may generate sufficient antibody response, but the relevance of this fact to public health decision making has yet to be clarified. The present study compares the risk of clinical attack (i.e. clinical attack rate) between one- and two-dose vaccination schemes. If the efficacies do not greatly vary between one- and two -dose schemes, one-dose vaccination may well be supported. Nevertheless, two-dose vaccination is shown to result in less morbidity if the vaccine efficacies are greatly diminished by reducing the dose. As long as the detailed efficacy estimates rest on theoretical assumptions, single-dose vaccination may only be sufficiently justified in a specific setting where the number of vaccines is extremely limited.

Introduction

As the world has experienced the global spread of the pandemic H1N1 influenza since April 2009, various pandemic vaccines have been manufactured around the world to reduce the incidence of the disease and to prevent severe illness and death. Since the number of vaccines that can be produced in parallel with a growing pandemic wave is limited, optimal timing of vaccination and prioritisation strategies have been sought to minimise the potential impact [1-3]. Results from early clinical trials have shown that a single dose of H1N1 vaccines probably generates antibody response at a sufficient level [4,5]. Following this early evidence, in United States it has been suggested that individuals aged ≥ 10 years receive a single dose [6]. However, although the early studies report immunogenicity (expressed as antibody titres) and safety of vaccination [4,5], their relevance to public health decision making has yet to be clarified. Taking into consideration that vaccines produced by various manufacturers differ in composition (e.g. adjuvanted and unadjuvanted vaccines), and optimal route of administration (i.e. intramuscular and subcutaneous injections), policymakers have faced the difficult choice whether to choose a one- or a two-dose regimen. The present study proposes a simple mathematical approach to deciding the optimal dosage of a pandemic vaccine by clarifying the population level implications of choosing either the one- or the two-dose vaccination scheme.

Methods

Theoretical basis

The number of doses of vaccine to use against the pandemic H1N1 influenza has not been established to date. Given that the antibody response to single-dose vaccination is not significantly different from that to a two-dose regimen (i.e. one dose on day 0 and another dose typically on day 21 or 28), the practical implication is that with one-dose alone we can vaccinate a population twice as large as that vaccinated with a two-dose regimen. In other words, given that the limited number of vaccines covers a proportion f of the population with a two-dose regimen, a one-dose regimen is expected to cover a proportion $2f$ with the similar efficacy. Nevertheless, the expected risk of clinical attack (i.e. which is equivalent to the so-called clinical attack rate or illness attack rate) at the end of an epidemic is influenced by herd immunity (which is non-linear), and most importantly, the actual protective effects of vaccination are unknown for both one- and two-dose schemes. Accordingly, we formulated our study question as follows: "Which should we implement, one- or two-dose vaccination, to minimise the risk of contracting influenza?" Whereas the optimal dosing of a pandemic vaccine against H5N1, accounting for continuous dose-response phenomena [7,8] has been discussed, our approach is different from previous studies in that we solely focus on two discrete doses, i.e., one- or two-dose regimens alone, analysing a wide range of relative efficacies for the one-dose regimen compared to two-dose scheme specifically against the pandemic H1N1 influenza virus.

Epidemiological model

Our arguments rest on a type of Kermack and McKendrick epidemic model. For mathematical convenience, and to offer simple arguments which are not case-specific (i.e. arguments which are independent of the ongoing pandemic waves), we assume that vaccination takes place sufficiently in advance of a pandemic. The numbers of unvaccinated and vaccinated new cases at calendar time t, $j_u(t)$ and $j_v(t)$, respectively, are described by the following renewal equations [9]:

(1)

$$j_u(t) = R_{uu}(t)\int_0^\infty j_u(t-s)g(s)ds + R_{uv}(t)\int_0^\infty j_v(t-s)g(s)ds,$$

$$j_v(t) = R_{vu}(t)\int_0^\infty j_u(t-s)g(s)ds + R_{vv}(t)\int_0^\infty j_v(t-s)g(s)ds,$$

where $R_{ij}(t)$ represents the average number of secondary cases in sub-population i generated by a single primary case in sub-population j at calendar time t, and $g(s)$ is the density function of the generation time. Linearising the system (1) near the disease-free equilibrium, we get the next-generation matrix:

(2)

$$K = \begin{pmatrix} R_{uu}(0) & R_{uv}(0) \\ R_{vu}(0) & R_{vv}(0) \end{pmatrix}$$

Let p_i be the vaccination coverage under an *i*-dose vaccination scheme (i = 1 or 2), $p_1 = 2p_2$ for $p_2 \leq 0.5$. There are two different types of efficacy which directly influence the transmission dynamics; i.e., reductions in susceptibility and in infectiousness, denoted by α_S and α_I, respectively. We assess the risk of a clinical attack in a homogeneously mixing population in which the next-generation matrix is simplified as

(3)

$$K = R\begin{pmatrix} (1-p_2) & (1-p_2)(1-\alpha_I) \\ p_2(1-\alpha_S) & p_2(1-\alpha_S)(1-\alpha_I) \end{pmatrix}$$

for a two-dose regimen, and

(4)

$$K = R\begin{pmatrix} (1-p_1) & (1-p_1)(1-k_I\alpha_I) \\ p_1(1-k_S\alpha_S) & p_1(1-k_S\alpha_S)(1-k_I\alpha_I) \end{pmatrix}$$

for one-dose regimen where R is referred to as the reproduction number, i.e., the average number of secondary cases generated by a typical infected individual at the initial growth phase of an epidemic. It should be noted that we do not use more widely known notation, the basic reproduction number, R_0 in light of the potential presence of immune adults before the pandemic. k_S and k_I, respectively, represent the relative efficacies of α_S and α_I for a one-dose regimen compared to a two-dose scheme (k_S, $k_I \leq 1$). The reproduction number under vaccination R_v is expressed as $R\{1\text{-}p_2\text{+}p_2(1\text{-}\alpha_S)(1\text{-}\alpha_I)\}$ for a two-dose scheme and $R\{1\text{-}p1\text{+}p1(1\text{-}k_S\alpha_S)(1\text{-}k_I\alpha_I)\}$ for a one-dose scheme.

Assuming that everyone without vaccination is susceptible before the epidemic, the proportions of those who have experienced infection by the end of the epidemic (i.e. final sizes) among unvaccinated and vaccinated individuals, z_u and z_v, are given by [10]:

(5)

$$z_u = 1 - \exp\left[-\left(R_{uu}(0)z_u + R_{uv}(0)z_v\right)\right],$$
$$z_v = 1 - \exp\left[-\left(R_{vu}(0)z_u + R_{vv}(0)z_v\right)\right].$$

Let b be the conditional probability of symptomatic disease given infection. The expected risk of clinical attack is expressed as $b[(1\text{-}p_i)z_u\text{+}p_i(1\text{-}\alpha_P)z_v]$ where α_P is the efficacy of reducing the probability of symptomatic disease, assumed to be independent of the transmission dynamics. We examine the sensitivity of the expected risk of clinical attack for different values of α_S, α_I and α_P by iteratively solving z_u and z_v in equations (5), where $R_{ij}(0)$ are dependent on the reproduction number (R), susceptibility effect (α_S), vaccine-induced reduction in infectiousness (α_I) and vaccination coverage (p_i).

Vaccine efficacy and other parameter values

The Table summarises parameter values that we extracted from literature. Although the reproduction number may vary across time and place as the subpopulations involved tend to vary greatly [11-17], we assume R = 1.5 as a common estimate in different settings [1,11,12]. The conditional probability, b, of developing symptomatic disease (given infection) has been suggested to be 66.7% [18]. Since vaccine efficacy estimates for the pandemic H1N1 influenza have yet to be reported, we adopt the estimates for seasonal influenza vaccines from an epidemiological analysis of metadata [19]. Conservatively, we assume that α_I and α_P following

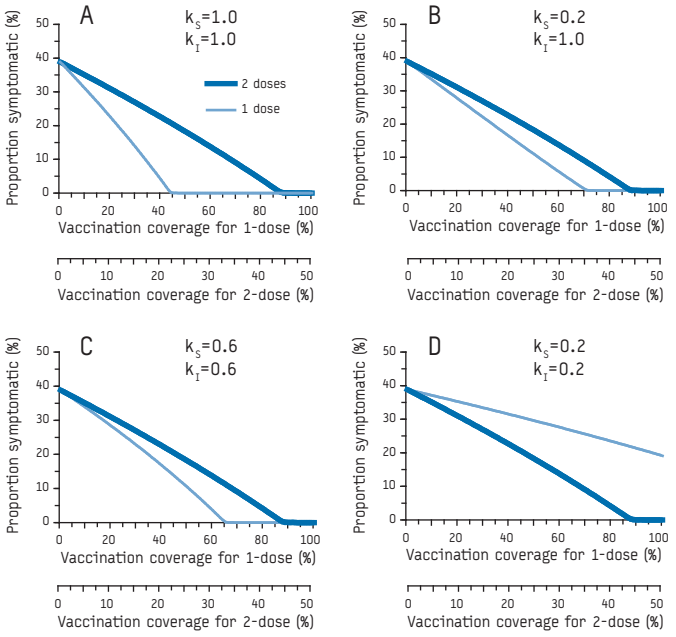
Table

Parameter values used for comparative risk assessment of vaccination against pandemic H1N1 influenza

Parameter	Value	References
Reproduction number (R)	1.5	[1,11,12]
Conditional probability of symptomatic disease given infection (b)	66.7 %	[18]
Reduction in susceptibility (α_S)	40.0%, 60.0%, 80.0%	Assumption and [19]
Reduction in infectiousness (α_I)	40.0 %	[19]
Reduction in the risk of contracting clinical disease (α_P)	67.0%	[19]

Figure 1

The expected risk of clinical attack as a function of vaccination coverage



Panels A-D compare the expected risks of contracting clinical disease between one- and two-dose vaccination schemes with different dose-related protective effects. The vaccination coverage (horizontal axis) for a one-dose regimen is twice as large as that for a two-dose scheme. k_S represents the relative efficacy (of one dose as compared to two doses) for reducing susceptibility, while k_I represents the relative efficacy of reducing infectiousness by the same dose reduction. The relative reduction in reducing the conditional probability of symptomatic disease (given infection) is assumed to be equal to that of infectiousness. The baseline parameters for a two-dose vaccination scheme are shown in Table, and the reduction in susceptibility α_S is assumed to be 0.6 for two-dose regimen.

a two-dose regimen are the same as those reported in [19] for inactivated vaccine (the estimates in literature are based on a one-dose regimen). We allowed α_S following two-dose vaccination to vary from 40% to 80% where the lower bound is equivalent to an estimate of meta-analysis based on one-dose scheme [19]. For a one-dose scheme, we assume that the susceptibility effect is reduced to $k_S\alpha_S$ where $k_S \leq 1$. Similarly, the reduction in infectiousness and the conditional probability of clinical disease given infection are reduced to $k_I\alpha_I$ and $k_I\alpha_P$ where $k_I \leq 1$; for simplicity we use the identical reduction factor for these two different types of efficacy.

Results

Figure 1A shows the baseline results of the risk of clinical attack as a function of vaccination coverage, assuming that the efficacies are identical between one- and two-dose vaccinations. In the absence of vaccination, 38.9% of the population is expected to experience clinical attack. If the efficacy estimates were identical, a one-dose vaccination could limit the impact using only half of the vaccine doses which are required for a two-dose scheme.

The superiority of a one-dose regimen is maintained even when k_S is reduced to 0.2 (with k_I = 1.0; Figure 1B), though the vaccination coverage needs to be higher to achieve the similar reduction of the risk of clinical attacks to that in Figure 1A. Even when both k_S and k_I are reduced (Figure 1C), this relationship (i.e. one-dose being superior) is still maintained. Nevertheless, when both k_S and k_I are greatly reduced (to 0.2; Figure 1D), a two-dose scheme becomes more efficient.

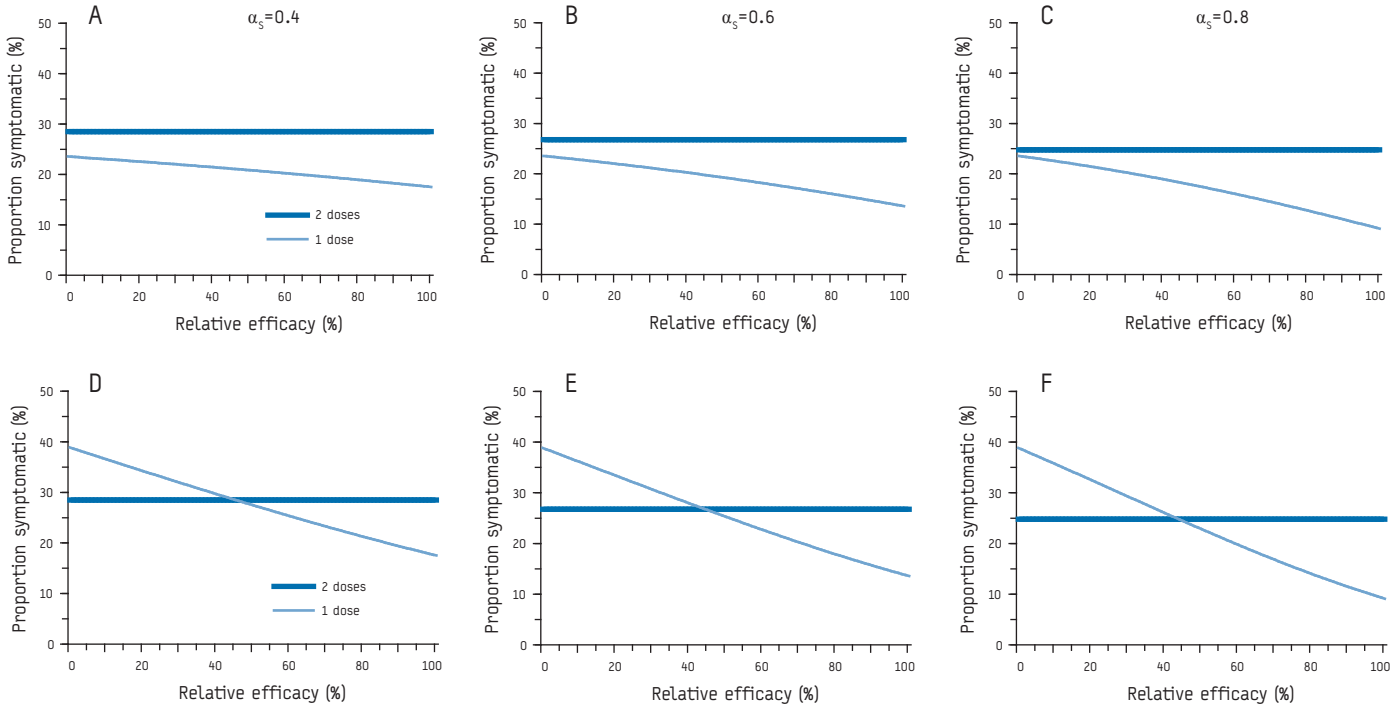
Figure 2 examines the sensitivity of the expected risk of clinical attack to different relative efficacy estimates (i.e. k_S and k_I) due to dose-reductions with fixed vaccination coverage under a one-dose scheme (30%). Figures 2A-2C compare the risk between one- and two-dose vaccinations, assuming that k_S alone varies with dose and k_I is fixed at 1.0. The expected risk with a one-dose scheme is more sensitive to k_S with a higher α_S estimate, but in general the superiority of a one-dose scheme is commonly seen. Figures 2D-2F compare the risks, varying both k_S and k_I simultaneously. If the dose-related relative reduction in efficacy is > 50%, a two-dose scheme yields a smaller risk of clinical attacks than a one-dose regimen. In addition, even when we discard the herd immunity effect (so that α_S and α_P alone would directly inform the frequency of clinical attack by $1-(1-\alpha_S)(1-\alpha_P)$), a two-dose scheme yields smaller risk than that of a one-dose scheme for the large dose-related relative reduction in efficacy. For instance, if α_S= 0.400 and α_P= 0.667, making k_I < 0.42 shows the two-dose regimen to be superior to the one-dose scheme.

Discussion

The present study compared the risk of clinical attack in pandemic H1N1 influenza under one- and two-dose vaccination

Figure 2

The expected risk of clinical attack as a function of the relative efficacy of vaccination as a result of a reduction in vaccine dosage



All panels compare the expected risks of contracting clinical disease between one- and two-dose vaccination schemes. In panels A-C, we assume that only the reduction in susceptibility is altered by reduction in the dosage of the vaccine. In panels D-F, all the efficacies (i.e. reductions in susceptibility, infectiousness and probability of symptomatic disease) are assumed to be equally reduced due to reduction in the vaccine dose. The baseline parameters for a two-dose vaccination scheme are shown in Table, and the reduction in susceptibility α_S is assumed to be 0.4 (A and D), 0.6 (B and E) and 0.8 (C and F) under a two-dose regimen. The vaccination coverage is fixed at 30% for one dose and 15% for two doses.

regimens, with an intention to assist relevant public health decision making. Instead of studying the impact of vaccination on reducing the probability of death among high risk groups (e.g. reducing the risk of death among those with underlying medical conditions), we employed a simple transmission model to find the optimal vaccination strategy which reduces the transmission itself. A single dose enables us to vaccinate twice as many people as a two-dose scheme can cover. Under the circumstances of an extremely limited number of vaccines, one-dose vaccination may well be supported if the efficacies do not greatly vary between one- and two-dose schemes. Although the dose-reduction for such a purpose (i.e. decrease doses to increase vaccination coverage) has not been recommended in the present pandemic because the number of vaccines is expected to increase over time [20], similar suggestions were given prior to the emergence of the H1N1 pandemic [7,8]. Moreover, exploring a wide range of relative efficacies for a one-dose regimen, the present study has also shown that a two-dose scheme may result in less morbidity if the vaccine efficacies are greatly diminished by reducing the dose.

An important technical message from the present study is that the relevant decision cannot be made by measuring antibody titres alone. Interpreting antibody titre usually forces us to adopt a well-known criterion, i.e. the haemagglutination inhibition titre > 1/40, as a correlate for individual protection [21], but this criterion itself has yet to be validated for the pandemic H1N1 influenza virus. Moreover, even if we can gain some practical insights into actual protection from the antibody titre, the validity of individual protection does not directly extend to the validity of herd immunity, which is more pertinent in respect to population level protection from infection. To understand the population level implications it is necessary to study in more detail the multidimensional protective effects of vaccination based on epidemiological studies [7,22], because an assessment of any infectious disease risks at the population level requires vaccine efficacy estimates which influence the transmission dynamics. Such efficacies include reductions in susceptibility, infectiousness and probability of symptomatic disease, as described in the present study.

The most difficult aspect of the ongoing pandemic H1N1 influenza is that we do not have an opportunity to analyse the abovementioned estimates in advance of vaccination practice. Moreover, the decision making for vaccination in the ongoing pandemic has to be done during the course of the pandemic waves [12]. In particular, one may prefer a one-dose to a two-dose scheme near the peak incidence of any pandemic wave to immunise as many susceptible individuals as possible. Nevertheless, as a practical implication of the present study, and as long as the detailed efficacy estimates rest on theoretical assumptions, one may consider that single-dose vaccination may be sufficiently justified only in a specific setting where the number of vaccines is extremely limited. At the same time, any observation of dose-related reduction in any biological action of vaccine efficacy (i.e. dose-related effects of reducing susceptibility and infectiousness) needs to be reported as soon as such an insight is gained during the course of the pandemic.

It should be noted that there are several limitations in the arguments we make here. First, parameter values in Table rest on theoretical assumptions, as the empirical estimates for H1N1 vaccines have yet to be clarified. Second, potential heterogeneity in vaccine efficacy must be noted as relevant. Efficacy estimates may differ between age- and risk- groups, as is the case for antibody responses [6,20], and this in turn may greatly influence decisions related to dosage for different age- and risk-groups. Third, we ignored heterogeneous patterns of transmission. In a heterogeneously mixing population, a one-dose regimen may not yield as large community benefit as presented in the present study, because the residual number of vaccines which were generated by reducing dosage from two-dose to one-dose may well be distributed to those with small risks of secondary transmission and severe manifestations.

There are several different pandemic vaccines (including those adjuvanted and unadjuvanted) with different routes of administration [23], and the efficacies of these are likely to be different. Thus, the decision on dosage cannot be made in a uniform theoretical fashion. Nevertheless, we believe that our simple approach satisfies the need to offer a basic insight into the question of vaccine dosage based on firm theoretical understanding.

Acknowledgements

The work of H Nishiura was supported by the JST PRESTO program.

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Pandemic influenza A(H1N1)v: human to pig transmission in Norway?

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This article was published on 12 November 2009.
Citation style for this article: Hofshagen M, Gjerset B, Er C, Tarpai A, Brun E, Dannevig B, Bruheim T, Fostad IG, Iversen B, Hungnes O, Lium B. Pandemic influenza A(H1N1)v: Human to pig transmission in Norway?. Euro Surveill. 2009;14(45):pii=19406. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19406

In Norway there is an ongoing outbreak in pigs of infections with pandemic influenza A(H1N1)v virus. The first herd was confirmed positive on 10 October 2009. As of 26 October, a total of 23 herds have been diagnosed as positive. The majority of the herds seem to have been infected by humans. Sequence analysis of pig viruses from the index farm shows that they are identical or virtually identical to human viruses from the same geographical region.

Introduction

The Norwegian pig herds have been considered free of swine influenza (the classical strain H1N1 and H3N2) as documented by a serological surveillance programme running since 1997 [1]. The pig industry in Norway is relatively small with approximately 2,700 herds and a little less than 1.5 million slaughtered animals in 2008.

Responding to the emergence of a novel influenza A(H1N1) strain (hereafter called pandemic influenza) affecting humans in April 2009, the surveillance of pandemic influenza in humans was initiated in Norway in late April, as a continuation and enhancement of the seasonal influenza surveillance systems. After the first detections of the pandemic influenza virus in Norway in early May, sporadic infections, mostly in travellers from abroad, increased gradually through the summer. After a peak in late July, the numbers declined while an increasingly larger proportion of cases were infected in Norway. A new increase has been seen through October and the cumulative number of laboratory verified cases by 26 October exceeded 3,300 [2].

There are reports from the World Organisation for Animal Health (OIE), on ProMED-mail [3] and in general media from other countries (Argentina, Canada, Australia, North Ireland, Ireland, United States) that human to animal transmission has occurred with the new pandemic influenza.

This paper describes an ongoing outbreak in pigs of infections with the pandemic influenza virus in Norway, providing insights on the source of infection and on the control strategies put into force for its control.

Detection of outbreak

On 9 October 2009, the Norwegian Food Safety Authority (NFSA) was contacted by a local veterinarian who informed about a possible outbreak of influenza in a pig herd of 85 sows and 850 growers and fattening pigs in Nord-Trøndelag County. In the period from 4 to 9 October a sow in the farrowing unit had been observed coughing. No other clinical signs of infection were observed in the rest of the herd and no animal had died. The NFSA was informed that a farm staff member had been ill with influenza-like symptoms (ILI) since 1 October, and tested positive for pandemic influenza virus on 8 October. The NFSA therefore decided to take nasal swabs from 20 pigs in the herd, and the samples were sent to the National Veterinary Institute (NVI) for analyses. On 10 October a total of 18 of the sampled pigs tested positive for influenza A and for 12 of these pandemic influenza viruses was confirmed.

An epidemiological investigation performed by the NFSA began on 11 October, and samples were collected from six additional herds located in close proximity to the index herd or with a history of close human/animal contacts. One of these, a herd with about 500 slaughter pigs, tested positive for pandemic influenza virus. This herd was owned by the infected animal handler of the index herd. This second herd positive for pandemic influenza was situated in an area with very intensive pig farming. Based on the possibility of a potential further airborne spread to neighbouring farms and with the aim to keep the Norwegian pig population free from swine influenza, it was decided to eradicate the second infected herd quickly. For animal welfare reasons and in spite of potential hazard for airborne spread during transport, all the pigs from this herd were transported to a nearby slaughterhouse and put down.

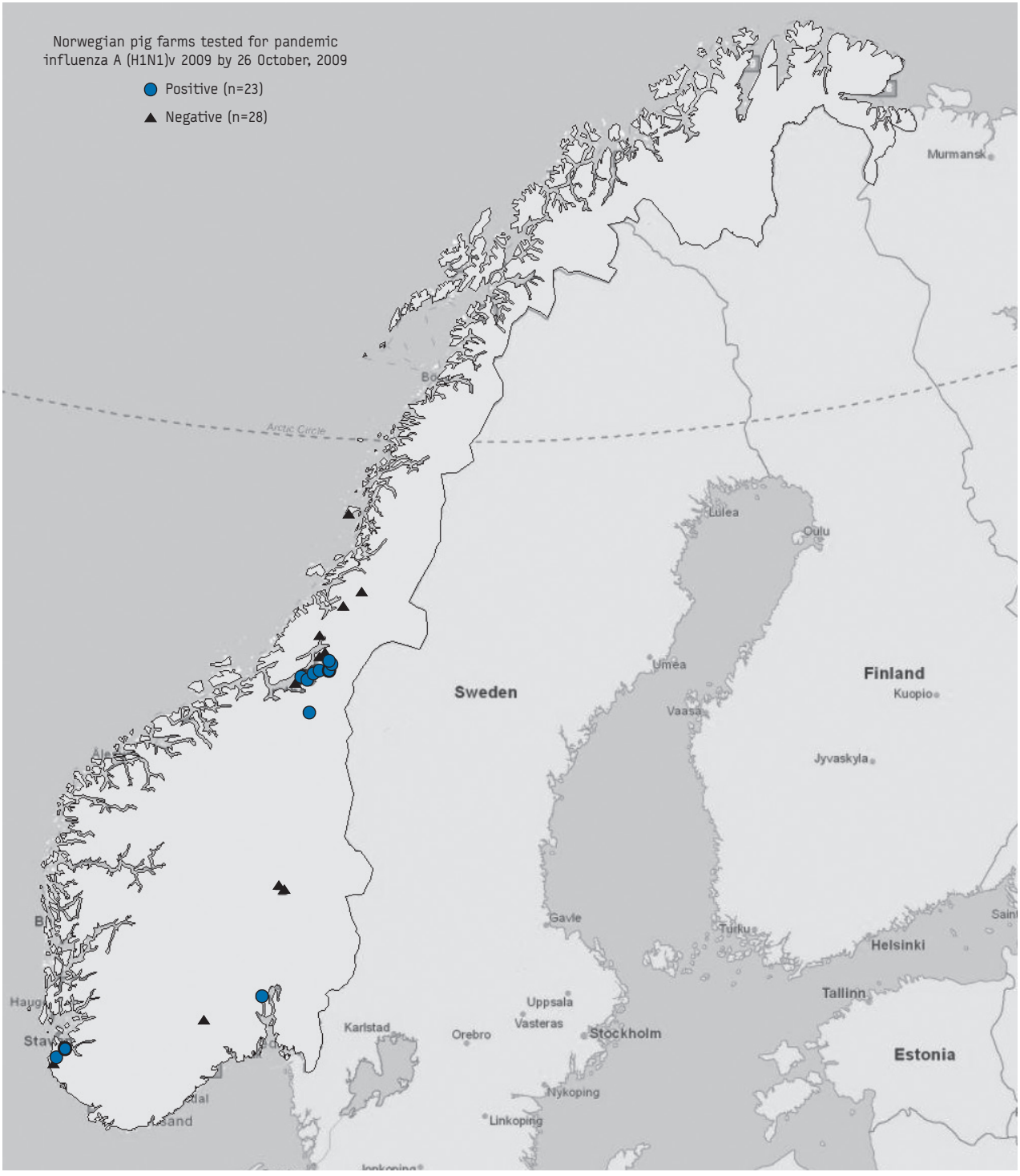
The plan was to slaughter the index herd during the same week. However, the eradication strategy was abandoned when four more herds in the area tested positive the next few days. It soon became clear that all the herds tested positive so far had been in contact with humans with ILI symptoms or with verified infection with pandemic influenza virus. At the same time, there was no evidence indicating there had been contact (pigs, staff, vehicles, etc.) between the new positive herds, and the possibility of airborne transmission was also ruled out due to long distances between the positive herds. Thus the sampling strategy was revised to include pig herds throughout Norway, having staff members with ILI or confirmed pandemic influenza, should be sampled. Later on, a revised surveillance programme for the Norwegian pig herds will be implemented.

Materials and methods

All herds except two, have been sampled by 20 nasal swabs. These swabs have been tested at the NVI by real-time RT-PCR to detect influenza A [4]. Samples positive in this test have also been tested for the pandemic influenza A(H1N1)v virus subtype [5]. The remaining two herds were sampled by 20 blood samples and

Figure

Pig herds tested for pandemic influenza A(H1N1)v virus, 10 October – 26 October, Norway, 2009 (n=51)



tested by enzyme-linked immunosorbent assay (ELISA, ID Screen® Influenza A Antibody Competition test, IDVET) and for subtype A(H1N1)v by haemagglutination inhibition test.

Results

In Nord-Trøndelag County, in the period between 10 October and 26 October, a total of 39 herds were tested and 18 of these were positive for pandemic influenza. Of these 18 positive herds, a total of 15 herds were in contact with people diagnosed with pandemic influenza (n=10) or with people with ILI symptoms (n=5). For the three remaining herds, there is no available information on such contact.

So far, in six of the 18 positive herds in Nord-Trøndelag County the clinical status of the herd has been recorded. Moderate clinical signs of influenza (coughing, fever) were recorded in four herds, while signs were mild to non-existing in two herds. In five of these six herds, the clinical signs in the pigs occurred after humans in contact with the pigs became ill.

In addition, during the period 12 October to 26 October, a total of 12 herds from six other counties were tested and five herds from three counties were positive for pandemic influenza virus. Also in these counties, the majority of positive herds are suspected of having contracted the virus from infected people.

The influenza virus in specimens taken from the index herd in Nord-Trøndelag has been sequenced at the Norwegian Institute of Public Health and compared to human strains from Norway and elsewhere, including the virus from the initial human case associated to the outbreak on this farm. The virus from two individual animals showed full identity in the two genome segments analysed for both pigs (full length H1 and 727 nt partial N1). There was also full identity to the 1,744 nt H1 gene of the virus from the farm staff member. Very high similarity was also observed to some of the viruses isolated from other humans in Norway, in particular to a virus found in the same geographical region. Within the entire 1,744 nt H1 and 727 nt N1 sequences compared, a difference in only one nucleotide in H1 was observed (99.9 and 100% identity, respectively). Full genome sequencing of the virus from one of the swine specimens confirms a very high similarity throughout the viral genome to the pandemic virus circulating in humans.

Discussion

In this investigation, humans infected with the pandemic influenza virus seem to be the most likely source for the spread of the infection to the pigs, even though additional routes, like airborne transmission or transmission by vehicles cannot be ruled out at the moment. So far, no evidence has suggested that animals play any particular role in the epidemiology or the spread of the pandemic influenza among humans. [6].

The Norwegian pig population has until this outbreak been free of classical swine influenza. The current situation thus presents an acute challenge for the pig industry and the NFSA. This has major long term implications for both the pig industry and for the public in terms of zoonotic potential. Transmission from humans to pigs and the possible vice versa is especially worrying. In addition pigs could potentially be effective multipliers for the virus, and might act as reservoirs of the virus during the out-of-season periods when the virus does not circulate in humans. Also, the virus could possibly further re-assort in case of swine or avian influenza viruses co-circulation, or mutate within the pigs to produce a more virulent strain [8]. The Norwegian authorities have taken several measures to control the outbreak such as monitoring the situation and the affected farms closely and restricting movements of animals from affected farms. Furthermore Norway follows the European Union working document [7] which recommends not slaughtering animals before at least seven days after the termination of clinical signs.

Further investigations are being carried out to clarify the extent of the outbreaks in the rest of Norway. Studies are also underway to evaluate risk factors for the infection at farm level. Farmers claim to maintain proper biosecurity as change of clothes and the use of face mask (surgical mask, gauze mask) before any contact with the pigs. However, due to lack of extra hands, on several occasions it had been necessary for the farmers to attend the pigs in spite of having influenza symptoms.

To further test the hypothesis that the pigs are infected by humans, follow up investigations should gather detailed information on directionality of transmission, such as what time point the farmer and the pigs showed signs of illness. To assist in such investigations, the results from nasal swabs taken initially and additional serological results should be further studied. Virus isolates from possible human and pig "pairs" are also available and can be further characterized.

Acknowledgements

Thanks to pig farmers throughout Norway informing about possible infected farms, to staff at the Norwegian Food Safety Authority for performing the sampling, to laboratory personnel at the National Veterinary Institute and the Norwegian Institute of Public Health in Oslo for performing the analyses and to the Veterinary Institute at Denmark Technical University for helping out with analyses of some of the samples.

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Assessing the impact of the 2009 H1N1 influenza pandemic on reporting of other threats through the Early Warning and Response System

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This article was published on 12 November 2009.
Citation style for this article: Cox A, Guglielmetti P, Coulombier D. Assessing the impact of the 2009 H1N1 influenza pandemic on reporting of other threats through the Early Warning and Response System. Euro Surveill. 2009;14(45):pii=19397. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19397

Since the start of 2009 H1N1 influenza pandemic, a notable surge in messages communicated through the Early Warning and Response System (EWRS) for the prevention and control of communicable diseases in the European Union has been recorded. In order to measure the impact of this increase on the reporting of other events, we compared the messages posted in the EWRS since April 2009 with those posted in the previous years (2004-2008). The analysis revealed that a ten-fold increase in messages was recorded during the pandemic period, from April to September 2009, and that the reporting of other threats dropped to a significantly low rate. These results suggest an important impact on the notification process of events in case of a situation requiring extensive mobilisation of public health resources. It emphasises the importance keeping an appropriate balancing of resources during sustained emergencies, in particular in view of a possible second wave of pandemic influenza cases, to ensure prompt detection and reporting of potential concomitant emerging threats.

Introduction

The Early Warning and Response System (EWRS) was created in 1998 under Decision No 2119/98/EC of the European Parliament and of the Council with the aim of establishing a permanent communication between the public health authorities of the European Union (EU) Member States (MS) responsible for planning and taking measures to control the spread of communicable diseases in the European Community. Under this decision, the MS are required to inform each other and the European Commission (EC) in order to coordinate public health measures to control events caused by communicable diseases of relevance for the European Union [1]. In addition, specific planning for pandemic influenza by the EC designates the EWRS system as the primary network used by the MS for exchange of information and coordination of measures during an influenza pandemic [2]. Since its establishment in March 2005, the ECDC has been supporting the EC by operating the EWRS.

Since the first cases of pandemic 2009 H1N1 influenza reported in the United States on 24 April 2009 [3], the MS, the EC and the ECDC have relied heavily on EWRS to communicate messages related to the pandemic, with a significant increase in the number of messages posted on EWRS compared with the same period of the previous years. The objective of this study was to analyse the use of EWRS from April to end of September 2009 and to assess the impact of the ongoing H1N1 influenza pandemic on reporting of other events to be notified through the EWRS under the EU legislation on communicable diseases.

Methods

The MS, the EC and the ECDC exchange information through EWRS using three types of communications: messages sent to all users, selective exchanges between two or more users, and comments to existing messages. For this study, EWRS activity was quantified using the term "new event" defined as a message posted for all users by any user. Selective exchange messages and comments were excluded.

New events were aggregated on monthly intervals from May 2004 through September 2009. Data prior to May 2004 were not included in the review because of a major change in the reporting system preventing historical comparisons. A descriptive analysis of the 65-month series was performed in order to observe reporting trends. Monthly reporting activity in 2009 was compared with averages of corresponding months over the five previous years (2004-2008). Events related to pandemic H1N1 influenza were then removed from the data set in order to focus the analysis on the reporting pattern of non pandemic-related events.

A Poisson test was used to quantify the decrease in notification of non-pandemic events as compared with the average notification for the same period in previous years. Averages were compared for months before and during the pandemic. A $p<0.05$ was considered statistically significant.

Results

The analysis of the 65-month series, totalling 917 new events, indicates a very sharp increase in recent months corresponding with the start of the pandemic H1N1 influenza. In addition, a smaller increase can be noticed during the first six months of 2006, corresponding to events related to the introduction of avian influenza (H5N1) to Europe. The average number of new events posted per month during the pandemic period of April to September 2009 was 68.0 versus 8.6 during the preceding five years, indicating an unprecedented increase in reporting during the pandemic period.

The average number of new events from 2004 to 2008 shows a seasonal pattern, with more new events being posted between June and October, on average. The maximum value observed in February 2006, 23 new events, corresponds to the avian influenza (H5N1) situation (Figure 1).

Significant deviation from expected seasonal reporting trends was observed during pandemic H1N1 influenza. Numbers indicated a dramatic increase in the total number of new events (n=120 in April 2009) and a historical low in the number of new events unrelated to pandemic H1N1 influenza (Figure 2).

The results of the Poisson probability test indicate that monthly event posting decreased significantly during March, June and July 2009 compared with the 2004-2008 averages (Table). These three months deviated from expected values with a $p<0.05$, indicating a significant decrease. Among the 48 new events reported in July, from 2004 to 2008, averaging 9.6 per month, 16 new events reported were related to food and water borne outbreaks (on average 3.2 per month), 8 were related to legionellosis cases (1.6 per month), 8 were related to vaccine preventable diseases (1.6 per month) and 16 were related to other conditions (3.2 per month).

Discussion

EWRS is known to be a very specific and reliable system, used to report confirmed events of European Community relevance requiring coordinated actions between the EU MS. EWRS has confirmed its value during the current pandemic, facilitating the necessary communications between MS, EC and ECDC to support implementation of rapid measures. However, on the basis of the results of our review, the dramatic increase in messages related to the current pandemic has masked a significant decrease in the reporting of other events. In July 2009, the number of non-pandemic related threads posted to EWRS dropped to zero. In August and September 2009, the number of new threads regained consistency with historical baseline values.

The decrease in March 2009 might be considered in the light of the high values reported in February and March 2006, related to avian influenza, which may have increased the historical baseline average value for these months. The significant decrease in the two consecutive months of June and July 2009 is extremely unlikely to be explained by chance alone.

In June and July 2009 several Member States were confronted with a dramatic increase in influenza cases. In this early stage of the H1N1 influenza pandemic, most Member States implemented a containment strategy aimed at preventing the introduction and community spread of the novel influenza virus. This strategy placed a tremendous strain on public health resources. During summer months, as cases tended to decrease during school holidays, most Member States discontinued active containment activities such as screening passengers and switched to a mitigation approach [4].

The concomitance of the dramatic decrease in notification of non-pandemic related threats during this period of extreme activity by national public health authorities suggests that the strain on

Figure 1

New events per month in the Early Warning and Response System (EWRS), May 2004 to September 2009 (n=917)

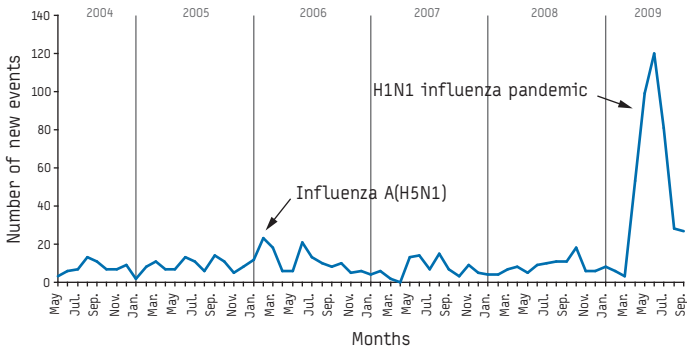
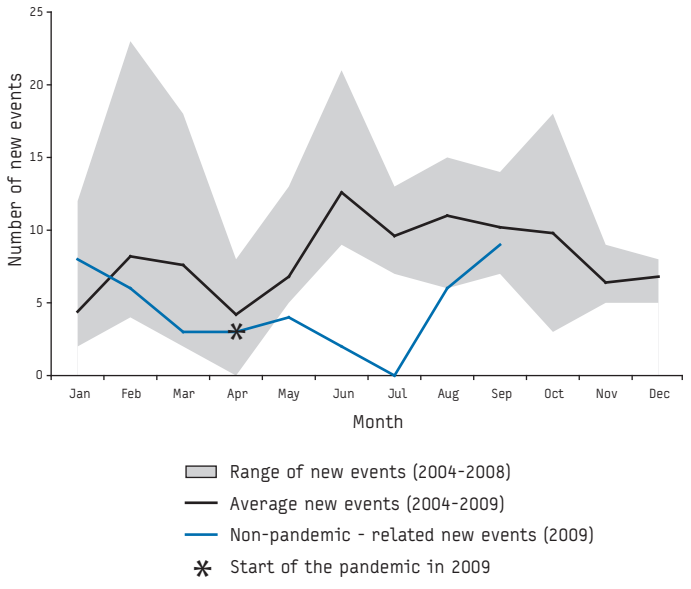


Figure 2

Monthly average and range of non-pandemic related new events in the Early Warning and Response System (EWRS) in 2004-2008 vs. number of new events in 2009



Table

Poisson probability test indicating significance of decrease in monthly threat reporting in the Early Warning and Response System (EWRS) during 2009 compared with 2004-2008 averages

Month	2004-2008 Average	2009 Number of new events (H1N1 influenza pandemic - related events excluded)	p-value
January	5.5	8	0.89
February	10.3	6	0.12
March	9.5	3	0.01*
April	5.3	3	0.23
May	6.8	4	0.19
June	12.6	2	0.0003*
July	9.6	0	0.00007*
August	11.0	6	0.08
September	10.2	9	0.43

* $p < 0.05$: significant value

public health resources had an impact on the notification process of other events. However, other factors may have contributed to the decrease. It is possible that a public health crisis such as the pandemic H1N1 influenza would result in a decrease of non-essential reporting of new events. Even if not thoroughly evaluated, the review of new events posted during historical baseline period does not indicate a significant reporting of non-essential events, such as events not fulfilling the criteria for notification through EWRS. In addition, it is unlikely that the pandemic H1N1 influenza would result in a true reduction of other threats at a time where relatively few cases were occurring in the EU.

In March and April 2003, a five-fold increase in reporting of new events was noted, in relation with the emergence of the severe acute respiratory syndrome (SARS) epidemic. However, no significant decrease in reporting of other new events was noticed in the EWRS (unpublished data). This could be due to the fact that SARS only affected several MS and responded well to control measures.

Conclusions

These findings highlight the need to maintain awareness of potential emerging threats, especially in the context of an ongoing pandemic. The sustained nature of a pandemic necessitates that those in charge of threat detection and response keep a high level of vigilance. In preparation for the expected second wave of pandemic H1N1 influenza in the European Union, it is important to consider the consequences of possible concomitant events, should they occur. This is an ideal opportunity to revisit current pandemic plans, taking into account appropriate allocation of resources to ensure an optimal level of vigilance.

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Botulism and hot-smoked whitefish: a family cluster of type E botulism in France, September 2009

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This article was published on 12 November 2009.
Citation style for this article: King LA, Niskanen T, Junnikkala M, Moilanen E, Lindström M, Korkeala H, Korhonen T, Popoff M, Mazuet C, Callon H, Pihier N, Peloux F, Ichai C, Quintard H, Dellamonica P, Cua E, Lasfargue M, Pierre F, de Valk H. Botulism and hot-smoked whitefish: a family cluster of type E botulism in France, September 2009. Euro Surveill. 2009;14(45):pii=19394. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19394

A family cluster of three cases of type E botulism were identified in south-east France in September 2009. The suspected food source of infection was a vacuum packed hot-smoked whitefish of Canadian origin purchased by the family during a visit to Finland and consumed several weeks later in France on the day prior to symptom onset. No leftover fish was available to confirm this hypothesis. Vacuum packed hot-smoked whitefish has previously been associated with cases of type E botulism in multiple countries, including Finland, Germany, the United States and Israel.

Case notification

A confirmed case of type E botulism in an individual residing in south-east France was reported to the French National Institute for Public Health Surveillance (Institut de Veille Sanitaire) by the National Reference Center (NRC) for Anaerobic Bacteria and Botulism at the Pasteur Institute in Paris on 10 September 2009. Two other members of the same family were reported as having clinical symptoms compatible with botulism. An investigation was undertaken to identify additional cases, the vehicle of transmission, and to put in place appropriate control measures.

Methods

Following notification of the cases, active case finding was carried out via contact with local health authorities, the NRC and the hospital services where cases were hospitalised. Hospital clinicians treating the patients, and thus likely to see other such cases, were reminded by telephone contact to immediately report all clinical suspicions of botulism to the local health authorities using the routine mandatory notification system for the disease.

Serum samples from the cases were analysed by the NRC. The presence of botulinum neurotoxin was confirmed by intraperitoneal administration of patient serum to mice, and the toxin type was ascertained by neutralisation with specific antibodies [1].

The food history of the cases in the three to four days before onset of symptoms was documented by the local health authorities, as were the details of purchase, transport and consumption of the suspected food product.

Based on patients' food history a fish product purchased during a family visit to Finland was suspected to have been the source of infection. A sample originating from the same batch of raw fish as the implicated product but processed one day later was collected from a local supermarket in Finland. The sample was sent to the Department of Food and Environmental Hygiene, University of Helsinki, Finland, for analysis of *Clostridium botulinum* by multiplex PCR targeted to the types A, B, E, and F neurotoxin genes [2]. Twelve 1gram samples from skin, gills or peritoneum were each inoculated into 10 ml of anaerobic tryptose-peptone-glucose-yeast extract (TPGY) medium and incubated at 30°C for three days. One ml of each culture was transferred to fresh TPGY medium and incubated overnight at 30°C. Lysed cells from 1 ml of each culture were used as template in PCR. PCR amplification products were visualised in 2% agarose gels against standard molecular weight markers.

Results

The three cases (two adults aged 52 and 46 years and one adolescent child aged 13 years) presented with classical clinical symptoms of botulism (gastrointestinal symptoms followed by

descending paralysis) on 7 September 2009 and were hospitalised the following day. One of the adult cases rapidly developed quadriplegia and required intubation and mechanical ventilation for 17 days. The other two patients presented with a milder form of the disease, did not develop paralysis of limbs or respiratory muscles and were released from hospital in mid-September. The severe case remained hospitalised as of 29 September (latest information available) but had regained motor function and begun to walk.

The NRC confirmed a diagnosis of type E botulism for the severe case. Botulinum toxin type E was identified in a serum sample (8 Mouse Lethal Dose/ml) and in two from three gastric juice samples (<20 MLD/ml). Serum samples from the two milder cases were negative for botulinum toxin. A faecal sample obtained from the child was negative for botulinum toxin and *C. botulinum*. No other botulism case associated with this episode was identified.

The food investigation carried out with the family identified the consumption of vacuum packed hot-smoked whitefish (*Coregonus lavaretus*) on 6 September 2009 (the day prior to symptom onset). All three sick members of the family reported having eaten the smoked fish and a fourth non-sick family member did not consume the product. There was no leftover fish to test for the presence of toxin. The family did not report consumption of any other foods usually associated with the risk for botulism (home-canned vegetables or home-prepared meat products such as ham, sausages and pâté) in the days preceding symptom onset.

The whitefish was purchased by the family in a supermarket in a village in east Finland on 22 August 2009. The fish was smoked in Finland but was originally from Canada. It was refrigerated after purchase. The family returned to France the following day. The fish was placed in a cooling bag with ice-packs for the duration of the 14-hour journey and then refrigerated upon arrival in the family home until the day of consumption on 6 September 2009, two days before the expiry date.

The fish was not heated prior to consumption. The entire product (800-1000 g) was eaten at the meal by the three patients. The adult with a severe form of the disease reportedly consumed a greater portion of the fish than the two milder cases.

An environmental investigation was carried out in the premises of the fishery production plant by the food control authority in Finland. The inspection focussed on the fish processing and storage temperatures, hygiene conditions and efficacy of in-house control of the producer. The storage temperature of the raw material, temperatures during the process and transport were found to be correct and in accordance with the in-house control plan and legislation. The raw fish was imported from Canada two months earlier and stored frozen at the premises' freezer (-18°C). The processing of the batch was started on 16 August 2009 with thawing and salting of the fish (temperature below 3°C). After hot smoking (two hours; maximum temperature 68°C) the fish was rapidly chilled (until 0.5° C), vacuum packed and stored below 3°C. The batch (about 600 kg) was transported at 0°C to the retail on 18 August 2009. The fish sample representing the same batch of raw material but processed one day later than the implicated fish product was negative for *C. botulinum* in the PCR analysis. Temperature controls carried out at the supermarket of purchase by the local food control authority showed storage temperatures for fishery products of 0.8-2.8°C.

Public health measures

European countries were informed of the event via the 'Early Warning and Response System' (EWRS) and an alert in the 'Rapid Alert System for Food and Feed' (RASFF), both issued on 11 September 2009. The information in the RASFF was subsequently transmitted to the Canadian food safety authorities. No other cases of botulism associated with this product were identified in Finland, France or other European Member States, as of 9 November 2009.

Discussion and conclusion

C. botulinum type E is an aquatic bacterium endemic in areas such as Canada and Alaska [3-5]. Type E botulism is characteristically associated with the consumption of improperly prepared foods of aquatic origin, either fresh water or marine [6]. Cases of type E botulism are very rare in France with the last episode declared in 2003 [7]. Foods associated with the occurrence of this form of botulism in France include salted herring, grey mullet, canned carp and canned sardines [8].

The negative mouse bioassay results of the serum samples of the two patients with a milder form of the disease could be explained by a lack of circulating toxin in the patients' blood. It is known that botulinum toxin cannot be detected in serum once it becomes irreversibly bound to its cell receptors and thus the detection of toxin in serum samples is believed to depend on the timeliness of sample collection and on the ingested dose of toxin, among other factors [6,9].

The epidemiological investigations support the hypothesis of the vacuum packed hot-smoked whitefish as the source of contamination of the three cases. No leftover fish was available for testing to confirm this hypothesis. An association between hot-smoked whitefish and type E botulism has been previously documented in Finland, Germany, the United States and Israel [10-13]. On two previous occasions, cases of type E botulism have been associated with whitefish imported from Canada and processed in Finland, as was the situation with the whitefish consumed by the three French cases [10,11].

Vacuum packed hot-smoked fish is a known risk food for type E botulism [14]. It is believed that the hot-smoking processes carried out on this type of fish, which typically reach temperatures of 60-80°C, are often insufficient to eliminate *C. botulinum* spores [15]. Among factors believed necessary for controlling growth and toxin production in this fish is the continuous storage of the fishery products below 3°C [10,11], information which is clearly labelled on this food product. According to the national legislation, modified atmosphere package (MAP) and vacuum packed fishery products must be stored below 3°C in production and at retail in Finland. Temperature controls carried out at the fishery production plant and the supermarket of purchase showed that storage temperatures were in accordance with the legislation. It is probable that the whitefish consumed by the three French cases was not stored below 3°C for the duration of the 14-hour return journey to France. Also, French domestic fridges are estimated to have an average temperature of 6.6°C [16] and thus well above 3°C. Assuming that the temperature of the family's fridge corresponds approximately to the estimated national average (the actual fridge temperature was not measured) the two weeks of refrigerated storage could have allowed ample time for growth and toxin production in the anaerobic environment created by vacuum packaging.

The absence of additional cases in Finland could be explained by a limited contamination of the whitefish by *C. botulinum*. The fish sample representing the implicated batch of raw material was negative for *C. botulinum* spores. In a previous case of human infection reported in Finland, 10 fish samples from an implicated batch were also negative for *C. botulinum* [11]. This is consistent with a previous prevalence study showing that 18% of raw and 5% of processed and packaged whitefish carry type E spores [14]. The absence of further cases may also be explained by a difference in storage habits of hot-smoked whitefish between the Finnish population and foreign tourists.

This family cluster provides further evidence of the risk of type E botulism associated with consumption of vacuum-packed hot-smoked whitefish. This episode also highlights the potential public health threat of *C. botulinum* spores in incorrectly stored processed food products and underlines the importance of clear labelling of storage conditions for products purchased in the refrigerated sections of supermarkets.

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First report of a North American invasive mosquito species Ochlerotatus atropalpus (Coquillett) in the Netherlands, 2009

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This article was published on 12 November 2009.
Citation style for this article: Scholte EJ, Den Hartog W, Braks M, Reusken C, Dik M, Hessels A. First report of a North American invasive mosquito species Ochlerotatus atropalpus (Coquillett) in the Netherlands, 2009. Euro Surveill. 2009;14(45):pii=19400. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19400

In late August and early September 2009, numerous larvae, pupae, and actively flying adult specimens of *Ochlerotatus atropalpus* were discovered in the Province of Brabant, southern Netherlands, during surveillance activities for *Aedes albopictus* at two trading companies that import used tires. No *Ae. albopictus* were found. Both companies mainly import used tires from countries in Europe, but also from North America. *Oc. atropalpus* is endemic to North America and has so far only been found outside of its endemic range in Europe, namely France and Italy, where it was subsequently eradicated. A preliminary modelling study shows that the weather conditions in the Netherlands are unlikely to prevent establishment of *Oc. atropalpus*. This species has so far only been shown to serve as a vector for virus transmission under laboratory conditions. Studies on potential human and veterinary health risks, as well as possible control strategies are currently ongoing.

Introduction

Following the discovery in 2005 of *Aedes albopictus* in the Netherlands at greenhouses of companies that import Lucky bamboo [1], surveillance activities to monitor this mosquito species were initiated. In 2006 a continuous surveillance programme was established and carried out by the Dutch Plant Protection Service (PPS) at these companies [2].

Gradually, other national surveillance activities for this mosquito species were established, including passive surveillance (since 2007) and active surveillance at parking lots along principle highways entering the country from the south and east (since 2008). The latter surveillance activity was initiated after reports of *Ae. albopictus* eggs found at parking lots in France, southern Germany, and Switzerland [3]. Since international trade of used tires is a well documented pathway dispersing *Ae. albopictus* around the world [4], surveillance at companies that import used tires was initiated in 2009. Except for the passive surveillance all *Ae. albopictus* surveillance activities are national surveys, carried out by the Plant Protection Service and funded by the Ministry of Public Health, Welfare, and Sports (Ministerie van Volksgezondheid, Welzijn en Sport, VWS).

During the surveillance at two companies that import used tires, the presence of *Ochlerotatus atropalpus* was observed at both companies. In Europe, the same species was found in Italy in 1996 [5] and in France in 2003 [6] and 2005 [7], but was eliminated in both countries by control measures directed against *Ae. albopictus* [8; F. Schaffner, pers. communication].

Methods

Two companies (subsequently called 'locations 1 and 2') were included in the survey. Both companies import used tires from airplanes, tractors, and large tires of rare sizes. One of the companies has two locations (location 2a and 2b). All three locations are in the south of the Netherlands, in the province of Brabant. All locations were inspected weekly.

Inspection of the sites consisted of checking tires for the presence of mosquito larvae and pupae, which were manually collected. Larvae collected during the first visit of location 1 were placed in alcohol and taken to the laboratory for molecular identification.

Larvae that were collected during the second and subsequent visits were either placed in alcohol and taken to the laboratory for morphological identification [9], or taken to the insectary to develop. A batch of eleven larvae was sent to an expert in mosquito taxonomy (F. Schaffner) at the University of Zurich, Switzerland, for morphological identification. Emerged adult mosquitoes were collected, identified morphologically, and stored in RNA-later tissue storage solution for future testing for viral RNA at the National Institute for Public Health and the Environment (Rijksinstituut voor Volksgezondheid en Milieu, RIVM). Molecular identification of the larvae consisted of sequencing the cytochrome oxidase 1 (CO1) gene, a mitochondrial gene with a relatively high mutation rate which renders it suitable for molecular species differentiation tests.

In total, 23 visits were carried out (eleven at location 1, eight at location 2a, and four at location 2b). On seven visits after the first inspection (three at location 1 and four at location 2a), the inspector was accompanied with a colleague who manually collected actively flying mosquitoes using hand-held mouth aspirators (transparent tubes with mesh wire to prevent inhalation of mosquitoes, used to capture live mosquitoes). These were brought to the laboratory, stored at -20ºC for at least one hour, identified morphologically, pinned, and labelled to be kept as reference material.

Additionally, after the first visit, 20 oviposition traps and several adult traps (three CO_2 traps with octenol and, at locations 1 and 2a, two additional BG Sentinel traps) were placed in the immediate surroundings of all three locations, in zones of approximately 1 km^2 to determine possible spread of the species.

In order to predict whether *Oc. atropalpus* could become established in the Netherlands, a modelling study was carried out using 'Climex' [10], a software designed to match climates in ecology, which is used to carry out rapid, reliable assessment of the risks posed by the introduction of different organisms and to predict locations to which they could spread and become established. Parameters (temperature, moisture, heat stress, dry stress, wet stress, and degree-days) for suitable areas for *Oc. atropalpus* establishment were based on parameters of the known original distribution area [11] and determined by adjusting these parameters until they fitted the original distribution area.

Results

First visit

Initially, only location 1 was inspected. During that visit, seven larvae were retrieved. Sequence results for the seven larvae were negative for *Ae. albopictus*. However, the sequence of the CO1 gene from all seven specimens matched to 98.6-99.0% the CO1 sequence of *Oc. atropalpus* stored in GenBank.

Second and subsequent visits

Identification of *Oc. atropalpus* at location 1 prompted further inspection visits to this location as well as visits to locations 2a and b. During the second visit at location 1, 11 Culicidae were collected. A taxonomy expert confirmed five of them as *Oc. atropalpus* by morphological identification (the others were *Culex pipiens* (n=5) and *Culiseta annulata* (n=1)).

Surveillance activities that were carried out in all three locations after the first visit (at location 1), resulted in the finding of numerous larvae and pupae. Approximately 500, 250, and 100 larvae were collected from locations 1, 2a and 2b respectively. At locations 1 and 2a, larvae were found in almost every tire that contained water. At these two locations, also actively flying adult mosquitoes were collected.

Oc. atropalpus was present at two of the three locations (locations 1 and 2a). Not all larvae collected have developed into adults yet, but from the data that have been analysed so far, approximately half of the emerged adults were morphologically diagnosed as *Oc. atropalpus.* The other were *Culex pipiens/torrentium* and, occasionally, *C. annulata.* The same is true for the actively flying adults that were collected. To date, no *Oc. atropalpus* eggs have been collected in any of the oviposition traps placed in the surrounding areas. Virus detection tests have yet to be carried out on the emerged adults stored in RNA-later solution.

At none of the three locations that were visited in this survey, *Ae. albopictus* was detected.

Climex model study

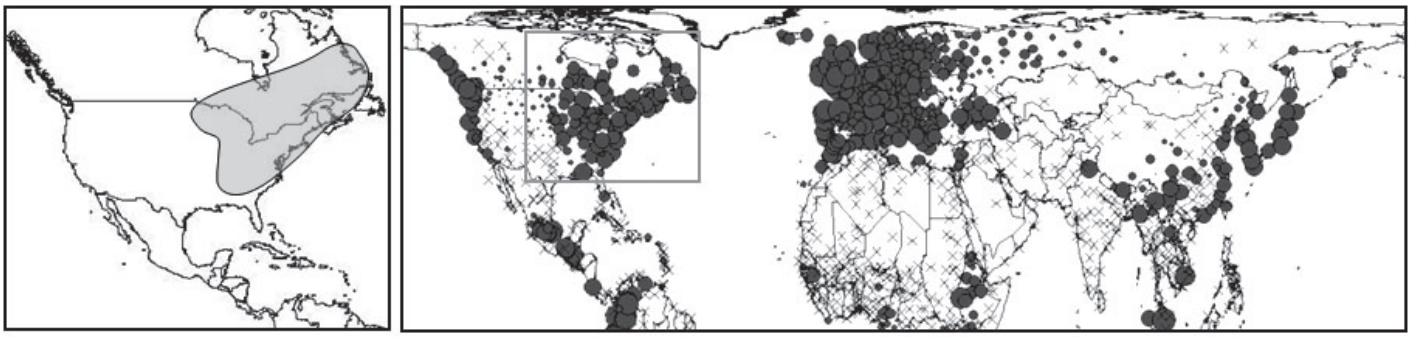
Using the 'match climates' module in 'Climex' software, parameters were set to fit the endemic geographic distribution of *Oc. atropalpus,* as described in [11] (southeastern Canada and mid-east-eastern United States). The model used this set of parameters to compare with meteorological data from locations in other areas of the world to predict likely areas where *Oc. atropalpus* could become established. This preliminary study shows that the climatological conditions in the Netherlands are not a limiting factor for establishment of *Oc. atropalpus* (see Figure).

Discussion and conclusion

The most likely introduction pathway of *Oc. atropalpus* from North America into the Netherlands is the passive transport of eggs through the import of used tires from airplanes, tractors, or soil-lifting vehicles. It is unlikely that the introduction has taken place this year, considering that tires containing *Oc. atropalpus* were found scattered over the premises of the two inspected companies, and only about 2% of the companies' tires are imported from overseas. Possibly, *Oc. atropalpus* was introduced several years ago. The fact that it was found in two different companies, separated by 100 km, could be explained by the fact that they occasionally exchange tires. Another possibility is that separate introductions

Figure

Climex model study for *Ochlerotatus atropalpus*



The grey area in Figure A shows the endemic geographic distribution of *Ochlerotatus atropalpus* [11; included here with permission from Journalof Genetics: Szymczak et al., 1986; J. Genet. 65(3):193-204, published by the Indian Academy of Sciences, Bangalore, India]. Areas with similar meteorological conditions as in the grey area (A) are depicted as dark grey dots in B (the larger the dot, the better the fit), thus predicting a relatively high likelihood that *Oc. atropalpus* could establish in that area. In contrast, crosses indicate areas with very low meteorological similarities to the area depicted in A, predicting that in such an area this mosquito species is unlikely to be able to establish.

of this species have occurred in the past. The species has been introduced into Europe on at least three separate occasions, once in Italy and twice in France, through import of used tires [5,6,7]. However, it is unlikely that the specimens found in the Netherlands were imported from other European companies since the three aforementioned known foci of *Oc. atropalpus* were successfully eradicated [8, F. Schaffner, pers. communication] and new introductions have not been reported since 2005.

The first results of the oviposition and adult traps in the surrounding areas of the two infested sites suggest that the species has not spread to the immediate surroundings. We are currently investigating whether the species (or other invasive mosquito species) are present at companies that import used truck and bus tires.

The results of the preliminary modelling study imply that *Oc. atropalpus* could become established in large areas of Europe.

In the field, *Oc. atropalpus* is not considered an important vector of infectious diseases. However, under laboratory conditions, the species is a competent vector for West Nile virus, Japanese encephalitis virus (JEV), Saint-Louis encephalitis virus (SLEV), La Crosse encephalitis virus (LACV), Murray valley encephalitis virus (MVEV), Western equine encephalitis virus (WEEV), and Eastern equine encephalitis virus (EEEV) [12,13]. SLEV and LACV can be transmitted transovarially by *Oc. atropalpus* [14,15], with laboratory studies that reported infection rates of up to 13.9% in adults that derived from eggs that were laid by LACV-infected females [15].

Oc. atropalpus was reported only once to be positive for virus infection: in one pool positive for WNV in the United States in the year 2000, out of 515 positive WNV pools consisting of 14 species [16]. It is possible that SLEV and LACV came into the Netherlands with the import of this mosquito species, but because of the limited role of *Oc. atropalpus* in the epidemiology of these viruses in its area of origin, this likelihood is considered very low. However, a role of the species in the spread of pathogens cannot be excluded.

The Dutch Ministry of Public Health, Welfare, and Sports considers this invasive mosquito species to be an 'unwanted organism' for the Netherlands, based on its putative role in the spread of infectious diseases important for public health. Control strategies are currently being investigated, including adequate treatment of used tires upon arrival and/or roofed storage of tires.

The aim of the surveillances at the tire import companies was initiated to monitor the presence of *Ae. albopictus.* The finding of *Oc. atropalpus* shows that other invasive mosquito species may be introduced as well and underlines the importance of mosquito surveillance systems.

Acknowledgements

We would like to thank F Schaffner (University of Zurich, Switzerland), G O'Meara (University of Florida, United States), G Majori (Istituto Superiore di Sanità, Rome), A Drago (Entostudio, Italy), T Howard (California Department of Public Health, United States), M Latham (Manatee County Mosquito Control District, United States), LP Lounibos (University of Florida, United States), M Van de Homberg (Centre for Monitoring of Vectors, the Netherlands), and S Bhagirath (Centre for Monitoring of Vectors, the Netherlands).

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Clostridium difficile ribotypes 001, 017, and 027 are associated with lethal C. difficile infection in Hesse, Germany

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This article was published on 12 November 2009.
Citation style for this article: Arvand M, Hauri AM, Zaiss NH, Witte W, Bettge-Weller G. Clostridium difficile ribotypes 001, 017, and 027 are associated with lethal C. difficile infection in Hesse, Germany. Euro Surveill. 2009;14(45):pii=19403. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19403

From January 2008 to April 2009, 72 cases of severe *Clostridium difficile* infection were reported from 18 different districts in the state of Hesse, Germany. A total of 41 *C. difficile* isolates from 41 patients were subjected to PCR ribotyping. PCR ribotype (RT) 027 was the most prevalent strain accounting for 24 of 41 (59%) of typed isolates, followed by RT 001 (eight isolates, 20%), RT 017 and 042 (two isolates each), and RT 003, 066, 078, 081, and RKI-034 (one isolate each). Eighteen patients had died within 30 days after admission. *C. difficile* was reported as underlying cause of or contributing to death in 14 patients, indicating a case fatality rate of 19%. The patients with lethal outcome attributable to *C. difficile* were 59-89 years-old (median 78 years). Ribotyping results were available for seven isolates associated with lethal outcome, which were identified as RT 027 in three and as RT 001 and 017 in two cases each. Our data suggest that *C. difficile* RT 027 is prevalent in some hospitals in Hesse and that, in addition to the possibly more virulent RT 027, other toxigenic *C. difficile* strains like RT 001 and 017 are associated with lethal *C. difficile* infections in this region.

Introduction

Clostridium difficile infection (CDI) is a major cause of morbidity and mortality from healthcare-associated infections in economically developed countries. CDI is primarily linked with hospital admission and prior antimicrobial treatment. The symptoms can range from mild diarrhoea to serious manifestations such as pseudomembranous colitis, toxic megacolon or perforation of colon [1]. In recent years, a hypervirulent strain, which has been characterised by pulsed field gel-electrophoresis as North American pulsed-field gel electrophoresis type 1 (NAP1) and by PCR as ribotype (RT) 027, has emerged in North America, Canada, and several European countries [2-6]. This strain has primarily been described in association with hospital outbreaks but may also cause community-acquired infection. RT 027 is characterised by production of *C. difficile* toxins A and B and a third toxin (binary toxin), deletions in the regulatory gene *tcd*C that potentially allow increased toxin A and B production, and resistance to new fluoroquinolones such as moxifloxacin [7,8].

In Germany, a hospital associated outbreak of the *C. difficile* RT 027 strain was reported in 2007 from Rheinland-Palatina in south-western Germany [9]. Since then, RT 027 has sporadically been isolated in other geographic regions of Germany [10]. A recent study found a high prevalence (55%) of *C. difficile* RT 001 in patients with *C. difficile*-associated diarrhoea (CDAD) in southern Germany [11]. Isolates corresponding to RT 001 did not contain the binary toxin genes *cdt*A and *cdt*B and displayed resistance to moxifloxacin and erythromycin [11].

In December 2007, a requirement for mandatory notification of severe CDI was introduced in Germany [12]. According to this requirement, severe CDI was defined as pseudomembranous colitis confirmed by endoscopy or histology, or CDAD or toxic megacolon with positive laboratory results for *C. difficile* associated with one of the following conditions:

- readmission to the hospital because of recurrent CDI,
- admission to intensive care unit because of CDAD or its complications,
- abdominal surgery because of toxic megacolon, perforation or refractory colitis,
- death within 30 day after CDAD, with CDI as underlying cause or contributing to death,
- detection of RT 027.

The Hesse State Health Office (HSHO) receives notifications on severe CDI from local health authorities of the state of Hesse, which is located in western Germany and has approximately six million inhabitants. Following the introduction of the federal notification requirement, we initiated a pilot study to characterise *C. difficile* isolates associated with severe CDI in Hesse by offering for free a complete microbiological diagnostic service including culture, toxin detection, antimicrobial resistance testing and ribotyping to those healthcare facilities in Hesse that do not have access to these analyses. In this report, we present the results of our study during the first 16 months after introduction of these measures.

Patients and methods

Study population

From January 2008 to April 2009, 60 patients with notifiable CDI were reported by local health authorities via electronic notification system (SurvNet) to the HSHO. A total of 24 *C. difficile* isolates from 24 of these patients had been submitted by the microbiological laboratories of the respective hospitals to a

national reference laboratory for *C. difficile* (Institute for Medical Microbiology, University of Mainz, or Robert Koch Institute (RKI), Wernigerode, Germany) for ribotyping. The ribotyping results of these isolates were reported to HSHO along with the case reports and corresponded in 23 of 24 cases to RT 027.

In addition, we received 22 stool samples from 17 patients with severe CDI that were sent to the microbiological laboratory of HSHO for detection and molecular typing of *C. difficile* during the study period. Comparison of the electronic notification reports with the data of these 17 patients revealed that 12 of them had not been reported by the electronic notification system. These cases were additionally enrolled in this study. The 17 patients were hospitalised in 13 different hospitals. Seventeen isolates (one isolate per patient) were forwarded to the national reference laboratory at the RKI for PCR ribotyping.

C. difficile culture, toxin analysis, and antimicrobial susceptibility testing

Faecal culture for *C. difficile* was performed on *C. difficile*-selective agar containing cycloserine, cefoxitin, and amphotericin B (Bio Mérieux) under anaerobic conditions. Identification of *C. difficile* was performed by routine microbiologic techniques and a rapid confirmatory latex agglutination test for *C. difficile* (Microgen Bioproducts). Twelve of 17 *C. difficile* isolates that were isolated in the HSHO laboratories were tested for in vitro toxin production with an ELISA detecting toxin A and/or B (Biopharm). Of the remaining five cases, four had been tested positive for toxin A/B directly from the stool specimen and were therefore considered to be toxin-positive. One isolate was lost because of fungal contamination and could not be used for ELISA or antimicrobial susceptibility testing. Sixteen isolates were subjected to susceptibility testing for erythromycin and moxifloxacin by E-test (AB-Biodisc).

PCR ribotyping

PCR ribotyping was performed at the RKI according the protocol of Bidet *et al.* [13], except that PCR Products were run on 1.5% agarose gels in 1× TBE at 85 volts for 4 h. Through cooperation with the reference laboratory for *C. difficile* at the Leiden University Medical Centre in the Netherlands and the German reference laboratory for gastrointestinal infections in Freiburg, the RKI accumulated a reference strain collection of 76 different *C. difficile* ribotypes, including 25 reference strains from the Cardiff Anaerobe Reference Laboratory in Wales, United Kingdom [14]. PCR ribotypes that differed from reference patterns by at least one band were assigned novel PCR ribotypes and marked with the prefix RKI [15]. Ribotyping at the University of Mainz was performed as described by Brazier *et al.* [6] by using the 25 reference strains from the Cardiff Anaerobe Reference Laboratory.

Results

Study population

From January 2008 to April 2009, a total of 72 severe CDI cases were reported to the HSHO by local health authorities or by clinicians in Hesse (Figure 1).

Thirty-eight patients (53%) were male and 34 (47%) were female. The patients´ age ranged from 30 to 94 years with a median age of 80 years (Figure 2).

The clinical symptoms included diarrhoea (72 cases), recurrent infection leading to hospital admission (19 cases), pseudomembranous colitis (nine cases), sepsis (five cases), colitis (two cases), and colon perforation, peritonitis and pancreatitis (one case each). Twenty-three of the cases were reported because

Figure 1

Cases of severe *C. difficile* infection reported from January 2008 to April 2009 in Hesse, Germany (n=72)

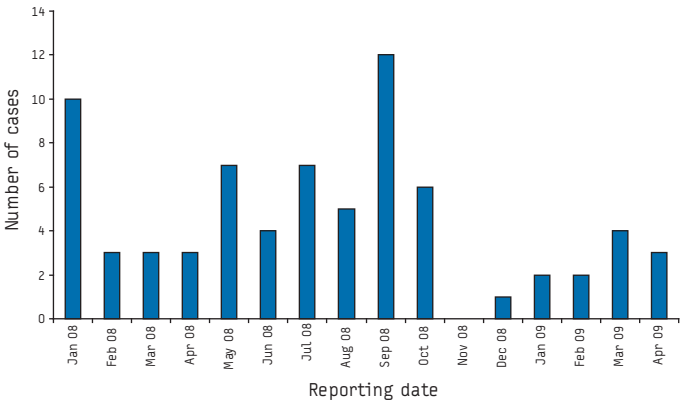


Figure 2

Age distribution of patients with severe *C. difficile* infection in Hesse, Germany (n=72)

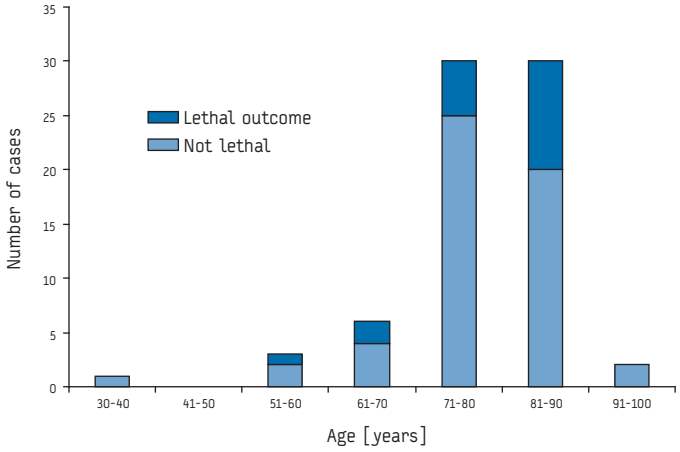
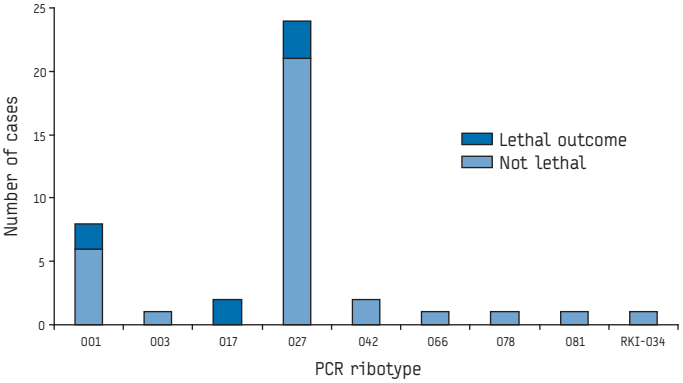


Figure 3

Assignment of *C. difficile* isolates collected from patients with severe CDI to PCR ribotypes, Hesse, Germany (n=41)



of detection of RT 027. The clinical outcome was disclosed in 60 cases (86%). The infection was lethal within 30 days after diagnosis in 18 cases (25%). Infection by *C. difficile* was reported as underlying cause of or contributing to death in 13 cases, and in one case as the most probable cause of death. The patients with lethal outcome that could be attributed to CDI were between 59 and 89 years-old, with a median age of 78 years.

PCR ribotypes, toxin production, antimicrobial susceptibility

Ribotyping results were available for 41 isolates obtained from 41 of the 72 patients with severe CDI. Twenty-four ribotyping results were reported to our institution via electronic notification system, while 17 isolates were isolated in the microbiological laboratory of our institution and forwarded for ribotyping to the national reference laboratory at the RKI. A total of 24 isolates were identified as RT 027, eight isolates as RT 001, two isolates each as RT 017 and 042, and one isolate each as RT 003, 066, 078 and 081. One isolate could not be assigned to any known RT and was designated as RKI-034 (Figure 3).

Production of toxin A and/or B was assessed in culture supernatants of the 12 *C. difficile* isolates cultured in our institution from patients with severe CDI. All isolates were tested positive for toxin A and/or B production. Interestingly, direct toxin detection in stool samples was negative in four of these 12 cases, confirming the higher sensitivity of culture compared to direct toxin detection in stool samples. Antimicrobial susceptibility results were available for 16 isolates. Six of the eight RT 001 isolates were tested and displayed resistance to moxifloxacin and erythromycin. Both RT 017 isolates, one of the two RT 042 isolates and the RT 078 isolate were resistant to moxifloxacin. Six isolates were susceptible to moxifloxacin. These results suggest that resistance to moxifloxacin is not a specific marker for RT 027.

Characterisation of *C. difficile* isolates associated with lethal infection

Eighteen (25%) patients had died during the hospitalisation period associated with severe CDI. Ribotyping results were available for seven of the cases with lethal outcome and identified RT 027 in three cases and RT 001 and 017 in two cases each (Figure 3). The clinical symptoms, previous antimicrobial therapy, and antimicrobial susceptibility results of these seven cases are summarised in the Table 1.

Discussion

In this study, we present the first results on surveillance of severe CDI in the state of Hesse with approximately six million inhabitants. A total of 72 cases of severe CDI were included in this study. Sixty cases were reported through the federal notification system, whereas 12 additional cases were enrolled because of our offer to analyse samples from patients with severe CDI in our diagnostic laboratory at no charge. Taking into account possible underreporting and the restricted use of microbiological diagnostic tools such as culture and ribotyping because of economic considerations, it can be hypothesised that the real incidence of severe CDI might be markedly higher in our region.

Sixty-nine (96%) of 72 patients included in this study were older than 60 years. The median age was 80 years. We observed a high rate (19%) of disease-related fatality in our study. Eleven of 14 patients with lethal outcome that was attributable to CDAD were older than 70 years. This finding is in accordance with the results of a recent study that identified advanced age (over 70 years) as a significant risk factor for illness and death among patients with CDAD [16]. However, it can not be ruled out that the emergence and circulation of epidemic and highly virulent *C. difficile* strain(s) may have contributed to an increased case fatality rate in our study.

Nine different *C. difficile* ribotypes were associated with severe CDI in our study. Ribotypes 027 and 001 were the most prevalent strains, while all other ribotypes were encountered only once or twice. Twenty-four of 41 typed isolates (59%) were RT 027. Since detection of RT 027 represents a case definition criterion for severe CDI in Germany, the high proportion of RT 027 may at least partially be attributed to a sampling bias. However, since the majority of RT 027 isolates were reported from a distinct district, a local outbreak in a particular hospital in that region can not be excluded. Further studies are required to evaluate this hypothesis. Taken together, our data show unequivocally that *C. difficile* 027 has emerged and is prevalent in Hesse.

Eight isolates (20%) were identified as RT 001 in this study. The high prevalence of RT 001 in our study is in accordance with

Table

Clinical data of patients with lethal *C. difficile* infection for whom isolates were available for analysis and ribotyping (n=7)

Patient, age, sex	Date of reporting	Hospital department	Clinical symptoms	Previous antimicrobial therapy	Erythro-mycin	Moxi-floxacin	PCR ribotype
Patient 1, 83, f	9 Mar 2008	medicine	CDAD, dialysis, hemi-colectomy,	ceftriaxon, clarithromycin, imipenem	n.d.	n.d.	027
Patient 2, 62, f	20 Mar 2008	medicine	CDAD, colitis, peritonitis	ceftriaxon, vancomycin, metronidazole	S	R	017
Patient 3, 86, m	22 Jul 2008	medicine	fracture, intracranial bleeding, dialysis, CDAD	ceftriaxon	n.d.	n.d.	027
Patient 4, 83, m	31 Jul 2008	medicine	urinary tract infection, CDAD, colitis	ampicillin-sulbactam	R	R	001
Patient 5, 73, f	9 Sept 2008	geriatrics	cystitis, CDAD, readmission	levofloxacin, vancomycin	n.d.	R	027
Patient 6, 72, m	10 Oct 2008	urology	gastroenteritis, CDAD	unknown, metronidazole	R	R	017
Patient 7, 59, m	11 Dec 2008	medicine	pseudomembranous colitis, sepsis	clarithromycin, amoxicillin, ampicillin-sulbactam	R	R	001

CDAD: *Clostridium difficile*-associated diarrhoea; n.d.: not defined; R: resistant; S: sensitive.

the results of Borgmann *et al*. who found a high prevalence (55%) of RT 001 in patients with CDAD in southern Germany in 2008 [11]. Thus, RT 001 appears to be a common *C. difficile* genotype in western and southern Germany. It is noteworthy that RT 001 used to be the most prevalent strain associated with hospital outbreaks in English hospitals in 2005, but its prevalence has declined to 7.8% of isolates in 2007-2008 [6]. Future studies are necessary to follow up the distribution of this ribotype in Germany.

One of the isolates in our study was identified as RT 078. An increased prevalence of CDI due to this ribotype in the Netherlands has been reported by Goorhuis *et al*. [17]. In the latter study, CDI due to both RT 078 and RT 027 presented with similar severity, but CDI associated with RT 078 affected a younger population and was more frequently community-associated. In our study, the patient suffering from severe CDI due to RT 078 was 60 years-old and therefore younger than the average. Our results indicate that RT 078 is prevalent in hospitals in Hesse. They are in agreement with the data by Rupnik *et al*. [18] who found RT 078 in 7.5% of *C. difficile* isolates collected from hospitals in Göttingen and the surrounding regions in the Lower Saxonia, Germany in 2006.

Ribotyping results were available for seven isolates associated with lethal CDI; three isolates were identified as RT 027, and two isolates each as RT 001 and 017. Our data suggest that, along with the hypervirulent RT 027, other toxigenic *C. difficile* strains such as RT 001 and 017 are associated with severe and lethal CDI in Hesse. It is noteworthy that ribotyping results were not available for half of the lethal cases of CDI in this study. Therefore, it is possible that also other ribotypes may be involved in severe CDI with lethal outcome. Our experience shows that offering the possibility to submit samples from patients with severe CDI to a specialised laboratory at no charge may help to collect more complete information.

In conclusion, the results presented here suggest that severe CDI is prevalent among hospitalised patients in Hesse. Severe CDI was associated with a high case fatality rate, especially in patients over 70 years of age. Nine different *C. difficile* ribotypes were associated with severe CDI. Lethal infections were observed in association with RT 001, 017, and 027. This study underlines the need for further studies on molecular epidemiology of *C. difficile*.

Acknowledgements

We thank the staff of local health authorities in Hesse for excellent cooperation. This project was supported by a grant of the Antibiotic Resistance Surveillance (ARS) programme of the German Federal Ministry of Health to WW.

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First set-up meeting for Antibiotic Resistance and Prescribing in European Children (ARPEC)

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This article was published on 12 November 2009.
Citation style for this article: Henderson KL, Müller-Pebody B, Johnson AP, Goossens H, Sharland M, on behalf of the ARPEC Group. First set-up meeting for Antibiotic Resistance and Prescribing in European Children (ARPEC). Euro Surveill. 2009;14(45):pii=19404. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19404

The Antibiotic Resistance and Prescribing in European Children (ARPEC) network, funded from January 2010 by the European Commission's Directorate-General for Health and Consumer Protection (DG SANCO), held its first set-up meeting at the Royal College of Paediatrics and Child Health, London, United Kingdom, on 15-16 October 2009. The collaborative group meeting was attended by 40 delegates from 17 Member States of the European Union (EU), and an invited expert from the European Surveillance of Antimicrobial Consumption (ESAC) project.

Young children are the main recipients of antibiotics in the EU with the majority of antibiotics given for minor upper respiratory tract infections [1]. There is clear evidence linking antibiotic prescribing to the development of antibiotic resistance [2]. Moreover, there are high rates of transmission of antibiotic-resistant pathogens among young children attending day-care in Europe [3]. If antibiotic prescribing in children could be reduced, selection and transmission of resistant strains in the EU should decrease. Although prudent antibiotic prescribing has been a high priority for the EU, there has been very little activity so far aimed at prescribing for children.

Although existing European surveillance schemes such as ESAC and the European Antimicrobial Resistance Surveillance System (EARSS) have some age-specific data, there is currently only very limited information on antimicrobial consumption and antibiotic resistance by children in Europe. The aims of the ARPEC project are:

- To use established methodologies from ESAC and EARSS and existing databases on community prescribing to develop a prospective surveillance system to monitor rates of antibiotic prescribing and resistance in EU children.
- To determine the variation in choice of drug, dose and indications for community and hospital antibiotic prescribing for common childhood infections between EU countries. For community paediatric prescribing the variation between countries in both overall and antibiotic class-specific rates will be determined. Even fewer data are available for comparative rates of antibiotic prescribing in children admitted to hospital.
- To produce a novel paediatric defined daily dose (DDD) methodology for comparison of hospital based antibiotic prescribing for children, as the current DDD guidelines are based on adult dosage.
- To conduct an EU-wide point prevalence survey to compare antibiotic use in children in hospital.
- To collect information on bacteraemia rates and antimicrobial susceptibility patterns for selected common pathogens in Europe in major children's hospitals in partner countries, using established EARSS methodology.
- To set early benchmarks for prescribing and resistance rates, working with clinical experts of the European Society for Paediatric Infectious Diseases (ESPID) to implement the benchmarks and encourage the development of prudent and more unified EU-wide treatment guidelines.
- To feed back the results of all projects to each country.

Individual data at hospital, regional and country level from a variety of the participating countries were presented and discussed by the group to explore the potential uses of the data for this Europe-wide initiative. There was great support from the representatives of the EU Member States to bring this project forward and build a stronger data flow system of paediatric antibiotic resistance and prescribing.

The expansion of the network by inclusion of other interested parties such as hospitals in the EU will also augment the available data to influence prescribing practices, as well as raise further awareness for ARPEC. If you would like to participate in the ARPEC project, please get in touch with the project leader, Dr Mike Sharland, at the Paediatric Infectious Diseases Unit at St. George's University of London: Mike.Sharland@stgeorges.nhs.uk

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News

The economic crisis and infectious disease control

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This article was published on 12 November 2009.
Citation style for this article: Suhrcke M, McKee M, Stuckler D, Suk JE, Tsolova S, Semenza JC. The economic crisis and infectious disease control. Euro Surveill. 2009;14(45):pii=19401. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19401

The economic crisis has challenged many deeply held notions about banks, markets and the financial sector. Concerns have also been raised that the economic crisis has the potential to affect the control of infectious diseases. Although there is agreement that the crisis will affect infectious disease control, there is disagreement about how. Some scientists have raised concerns that both emerging infectious disease threats, such as the H1N1 pandemic, as well as longstanding challenges, such as control of tuberculosis, HIV/AIDS and their drug-resistance strains, could suffer if communicable disease control budgets are cut. They point to the rises in HIV/AIDS and tuberculosis that occurred in former communist countries in the 1990s.

Thus far, evidence on the effects of crisis on infectious diseases in general is limited. As the current crisis unfolds, it will be crucial to continue the work with identifying emerging infectious disease risks and control them rapidly before they develop into population-wide threats.

How the economic crisis is impacting on communicable disease surveillance and control in European Union (EU) and European Free Trade Association (EFTA) countries is the subject of a study being undertaken by European Centre for Disease Prevention and Control (ECDC) in collaboration with a team from the University of East Anglia and the London School of Hygiene & Tropical Medicine.

In order to help us gather data, please complete a short on-line questionnaire available at: http://www.surveymonkey.com/s.aspx?sm=SoCRzEG2oYgZOoNCDH8G_2bQ_3d_3d

This should take no more than 30 minutes of your time. It is important to gather as much relevant information as possible so any assistance you can provide in answering this questionnaire will be extremely valuable. All responses will, of course, be treated as confidential but if you permit we may come back to you with questions for clarification of points that arise.

If you have any questions, please contact Sandra Alves (email: Sandra.Alves@ecdc.europa.eu).